The feasibility of monitoring exercise intensity in mechanically ventilated patients recovering from critical illness in Intensive Care

Claire Black

University College London

Thesis submitted for the award of the degree of

Doctor of Philosophy

Declaration

I, Claire Black confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed.....

November 2015

Acknowledgements

I have learnt and achieved far more in the last six years than could ever be documented in these pages. For this I am indebted to many people and many organisations. My supervisors; Prof. Mervyn Singer, not only for his boundless enthusiasm and belief that I could embark on and complete this PhD, but his inclusion of everyone who steps foot into his lab, and Prof. Mike Grocott for his guidance and whose timely reality checks were well-founded. To the NIHR, for funding my clinical doctoral research fellowship and giving me the opportunity to investigate an area of my clinical life I am so passionate about. To Victor Ford and Dr. George Latter at UCH, both now retired, for their technical advice in the early stages. Dr. Stewart Laing from the British Olympic Medical Institute for sharing his expertise on the Douglas Bag technique. Dr. Parvis Habibi, for the loan of the Deltatrac, a device I begrudgingly came to admire. To Alison Gordon, Nikki Webster and the ICU team at UCH for making the data collection possible. To all the patients and their families who participated with such enthusiasm and interest.

To the friends I made in the Singer Lab over the years; Saima Saeed, Bernardo Bollen-Pinto, Alex Dyson, Neil Hill, Nas Ekbal, Nish Arul, Steve Harris, Vic Khaliq, Anna Lac and Anna Kleyman, I owe you my sanity.

To Zac for his humorous acceptance of my "doing work". And finally to Bruce; sounding-board, proof reader and without whose unwavering support none of the following would have been possible. Thanks for putting up with me.

Data analysis acknowledgements

All data was analysed using R [1]. The graphs were plotted using ggplot2 [2], scatterplot3d [3], RColorBrewer [4], gridextra [5] and lattice [6]. The tables were generated using plyr [7], xtable [8], texreg [9] and tidyr [10]. Statistical analysis was carried out using lme4 [11], influence.ME [12], PredictABEL [13], pROC [14], caret [15], e1071 [16] and merTools [17].

Abstract

Critical illness survivorship is frequently characterised by profound long-term physical and psychological disabilities. These arise as a result of the complex interaction between the patho-physiological effects of critical illness, clinical interventions and the impact of prolonged bed rest on physical and psychological health. Early rehabilitation in the ICU is an important intervention that can overcome some of the devastating impacts of critical illness on patients and their carers.

However, with little or no scientific basis for its prescription and no validated means of assessing individual patient workload during rehabilitation, a "one-size-fits-all" approach is generally adopted. In contrast, the field of sports science has an extensive literature base describing the optimisation of individual training programs. This thesis explores the potential translation of key precepts of exercise physiology into the ICU setting in order to quantify the workload during rehabilitation in mechanically ventilated (MV) patients recovering from critical illness. Breath-by-breath-gas-exchange-analysis (BBGEA) is the gold standard for measuring exercise capacity and intensity in non-ventilated individuals. However, validated devices in MV patients are lacking.

In this thesis the MedGraphics Ultima, a BBGEA device, was validated in the critical care setting, within the limits of two reference techniques; Douglas bag collection and Deltatrac II. The feasibility of using BBGEA in patients rehabilitating in the ICU and the oxygen cost of this rehabilitation were then investigated. I established that, while this device is an invaluable research tool, it is impractical for day-to-day clinical practice. I further identified that the oxygen cost of rehabilitation activities in the ICU is not directly activity-dependent. I then developed two models to generate proxy values of oxygen consumption, during rehabilitation interventions, evaluating their performance with a small validation sample.

The huge variations in the exercise load of rehabilitation interventions between and within patients highlights the need to establish personalised exercise regimens.

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Acronyms

Acronym	In Full
ABG	arterial blood gas
ABP	arterial blood pressure
ADL	activities of daily living
AIC	Akaike's information criterion
ALI	acute lung injury
ANOVA	analysis of variance
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	acute respiratory distress syndrome
AT	anaerobic threshold
ATP	adenosine triphosphate
BBGEA	breath gas exchange analysis
BCT	bed chair transfer
BDNF	brain-derived neurotrophic factor
BI	Barthel Index
BIC	Bayesian information criterion
BMI	body mass index
BNB	blood nerve barrier
bpm	breaths per minute
CHD	chronic heart disease
cHRmax	calculated heart rate max
CI	confidence interval
CIM	critical illness myopathy
CIP	critical illness polyneuropathy
CIPNM	critical illness polyneuromyopathy
CKD	chronic kidney disease
cmH_2O	cm of water

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Acronym	In Full
CMV	controlled mandatory ventilation
COPD	chronic obstructive pulmonary disease
CRP	C reactive protein
CSA	cross sectional area
CT	cognitive therapy
$D_2{}^{18}O$	deuterium oxide
DBC	Douglas bag collections
DNA	deoxyribonucleic acid
DTII	Deltatrac II
ECG	electrocardiography
EMG	electromyography
EMS	electrical muscle stimulation
IGF-I	insulin-like growth factor 1
EPOC	excess post exercise oxygen consumption
EQ-5D	Euro Qol 5 dimensions
FAC	functional ambulatory category
FFT	fast Fourier transformation
FIM	functional independence measure
F_iO_2	fraction of inspired oxygen
GESV	gas exchange system validators
GPPAQ	general practice physical activity questionnaire
Hb	haemoglobin
HME	heat moisture exchanger
HR_{rec}	heart rate recovery
HFP	high frequency power
HR	heart rate
HR_{max}	heart rate max
HR_{res}	heart rate reserve
HRpeak	heart rate peak
HRQOL	health-related quality of life
HRrec	heart rate recovery
HRV	heart rate variability
ICF	international classification of functioning
ICU	Intensive Care Unit

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Acronym	In Full
ICU-FSS	ICU functional status score
ICUAW	ICU-acquired weakness
IQR	interquartile range
LFP	low frequency power
LOS	length of stay
NBP	non-invasive blood pressure
MDT	multidisciplinary team
MET	metabolic equivalent
MGU	Medical Graphics Ultima
MODS	multi organ-dysfunction
MOS	marching on the spot
MRC sum score	medical research council sum score
MROC	multi class receiver operated characteristics
MRT	median response time
MS	mass spectroscopy
MV	mechanical ventilation
NPV	negative predictive value
OBLA	onset of blood lactate accumulation
^{18}O	oxygen-18
$P_{ET}CO_2$	end tidal carbon dioxide
PFIT	physical function ICU test
PGC1-α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PS	patient side
PSinc	pressure support increment
PMV	prolonged mechanical ventilation
PPV	positive predictive value
PR	pulmonary rehabilitation
PS	pressure support
PT	physical therapy
PTSD	post traumatic stress disorder
RBANS	repeatable battery for the assessment of neuropsychological status
RCT	randomised controlled trial
REE	resting energy expenditure
RER	respiratory exchange ration

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Acronym	In Full
RICU	respiratory intensive care unit
RLD	rate limiting drug
RPE	rate of perceived exertion
RPM	revolutions per minute
RQ	respiratory quotient
SD	standard deviation
SF-36	short form-36
SIMV	synchronised intermittent mandatory ventilation
SIRS	systemic inflammatory response syndrome
SOEB	sit over the edge of the bed
SOFA	sequential organ failure assessment
STS	sit to stand
TNF-α	tumour necrosis factor
TP	total power
TUG	timed up and go
UC	usual care
UCH	University College Hospital
UCLH	University College London Hospitals
$\dot{V}_E$	minute ventilation
VCO_2	volume of carbon dioxide produced
VO_2	volume of oxygen consumed
VS	ventilator side
VT	tidal volume
$\dot{V}CO_2$	rate of carbon dioxide production
$\dot{V}O_2$	rate of oxygen consumption
WCC	white cell count
^2H	deuterium
6MWD	6 minute walk distance

Chapter 1

Introduction

Since Margaret Herridge's landmark paper [18] on the poor physical outcomes of 109 ARDS survivors, numerous papers have described the experience of surviving critical illness [19–23]. These reports highlight survivorship as a significant challenge facing the critical care community [24]. Characteristically, the complex interaction of physical, cognitive and mental health sequelae render patients immobile, reliant on carer support for activities of daily living, unable to process simple information and frequently suffering post-traumatic stress syndromes. The development of rehabilitation strategies to overcome the devastating legacy of critical illness on its survivors and their carers has become a priority within the critical care community. Particular attention is being paid to promoting early activity within the ICU. The expectation is to minimise the patho-physiological effects of critical illness, its subsequent therapies and the impact of prolonged bed rest on short and long-term functional outcomes.

The absence of a theoretical framework for the mechanisms of injury and recovery continues to hinder the development of preventative strategies and the design of appropriate later interventions. So with little or no scientific basis for its prescription, clinicians are compelled to take a pragmatic approach to the rehabilitation of patients recovering from critical illness. We can not accurately identify those patients who have the multi-system capacity to respond to rehabilitation interventions. Nor can we identify the intensity or duration of the intervention that will have the most value for an individual patient. Moreover, having provided the intervention, we have yet to identify a consistent way to measure outcome [25].

This thesis aims to address just one of these issues; how to quantify the intervention of rehabilitation. Given that many rehabilitation interventions are probably dose-responsive, regardless of the underpinning mechanism, it is a reasonable assumption that most patients enrolled in interventional studies and, indeed, receiving rehabilitation in the acute setting, are

either being under or over-trained. This raises very real questions for clinicians; How do we get the training load right for each of our mechanically ventilated patients? How do we ensure we do not over-train some patients, potentially slowing their weaning, physical and psychological recovery, while not under-training others, holding them back and not allowing them to reach their full potential?

My overall aim is to establish a method of quantifying rehabilitation interventions in mechanically ventilated patients with, and recovering from, critical illness in the ICU.

My objectives are.

Objective 1: To validate a medical device to measure oxygen consumption in mechanically ventilated patients.

Objective 2: To develop a standardised reproducible exercise stimulus.

Objective 3: To identify a method of quantifying rehabilitation interventions.

Objective 4: To validate the exercise quantification tool.

In this thesis I shall first provide an overview of survivorship following critical illness and the role that deteriorating physical function takes in the subsequent disability experienced by the patient. To better inform the theoretical framework for prevention of deterioration or recovery of physical function, I shall then take a closer look at impairments that lead to these physical function deficits, highlighting the need to quantify rehabilitation interventions. Following on from this I will review the rapidly growing literature on rehabilitation in the acute care setting in the context of global variations in both clinical practice and cultural ICU differences, and then this literatures translation into practice. Having recognised the need for a validated tool to quantify rehabilitation interventions, I shall then review possible techniques of doing this in mechanically ventilated patients, identifying one method; breath-by-breath-gas-exchange-analysis (BBGEA), as worthy of further investigation. The fourth chapter covers validation of the BBGEA equipment in the critical care setting, with a section on the challenges using this technique in mechanically ventilated patients. The fifth chapter investigates the feasibility of using this technique in patients rehabilitating in ICU and the oxygen cost of this rehabilitation. The sixth chapter deals with a potential way to quantify rehabilitation interventions using BBGEA, its translation into clinical practice and a small validation sample of the models created. The final chapter draws all this together and looks to future work.

Chapter 2

Physical function following critical illness

2.1 Survivorship following critical illness

In 2003 Margaret Herridge published her landmark paper on the physical outcomes of 109 acute respiratory distress syndrome (ARDS) survivors [18]. Numerous papers describing the experience of surviving critical illness have since been published [19–23]. These reports highlight survivorship as a significant challenge facing the critical care community [24]. Characteristically, the complex interaction of physical, cognitive and mental health sequelae render patients immobile, reliant on carer support for activities of daily living, unable to process simple information, and frequently suffering from post-traumatic stress syndromes.

2.1.1 Sub-cohorts

The all-encompassing term of ICU survivorship accommodates several sub-cohorts of patients with different long-term survival rates, rehabilitation trajectories, caregiver burdens and ongoing health care costs [26]. A crude but none-the-less pragmatic way to stratify patients has been put forward by Kress and Herridge [27]. They suggest a continuum of worsening physical disability from young ARDS through "chronic critical illness" to "debilitated elderly". Essentially, poorer outcomes are seen with increasing physiological age.

2.1.2 Survival

Hospital and one year survival following mechanical ventilation for critical illness depends on various factors such as the patient's age, comorbidities, underlying condition and the duration of mechanical ventilation. Only 33% of elderly patients $\geq$65 years survive to hospital discharge

[28], compared to 60% of ARDS patients with a mean age of 47 years [18] and 71% of prolonged mechanical ventilation (PMV) patients with a mean age of 55 years [29]. At one year, survival is 22%, 50% and 55% respectively for each cohort. Chronological age is a controversial predictor of survival from critical illness [30, 31]. However, physiological age, accounting for the co-morbidity burden, physiological reserve and the trajectory of health prior to the critical illness, may be much more important [26].

2.1.3 Health-Related Quality of Life

A systematic review of health related quality of life (HRQOL) during post-discharge follow-up, published in 2005, found ICU survivors had significantly lower HRQOL scores than the general population in all SF-36[1] domains. After 12 months, 2 of the 4 studies reviewed, found clinically meaningful improvement in each SF-36 domain except mental and general health perceptions. The majority of studies found that age and severity of illness predicted adverse physical function outcomes [32]. A more recent review [33] found that survivors of critically illness had a lower HRQOL than an age and gender-matched population. Interestingly, HRQOL differed according to the patients diagnostic category. The most significant reductions in quality of life were seen in patients with severe ARDS, PMV, severe trauma and severe sepsis.

2.1.4 Physical function

A consistent feature of survivorship from critical illness is the profound deterioration in long-term physical function. The extent and trajectory of recovery is modulated by numerous factors [26, 33, 34]. Herridge's original report described a group of ARDS survivors with median six-minute walk distances (6MWD)[2] that were 49%, 64% and 66% of predicted at 3,6 and 12 months post-discharge, respectively. Later follow-up revealed ongoing physical function problems at 5 years, with median 6MWD still only 76% of predicted [35]. Subsequent studies of similar cohorts have also demonstrated similar outcomes, with a relative plateau in recovery of the physical outcome measures at 12 months post-acute lung injury (ALI) [35–39]. In contrast, in a cohort of 126 patients who received ventilation for >4 days with a tracheostomy, or >21 days without, of those alive at one year, only 9% had no functional dependency, 26% had moderate dependency, while 21% had complete functional dependency [29].

The impact of pre-illness functional status on long-term outcomes has been borne out in a number of papers. In a prospective Spanish study of 230 previously healthy, elderly patients

[1]The Short Form-36, is a 36-item, patient-reported survey of patient health. There are eight sections; vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

[2]6MWD, the distance that a patient can walk on a flat, hard surface in a period of 6 minutes.

(≥65 years), with a Barthel Index (BI)[3] score ≥75, and without cognitive impairment, only 112 (48.9%) were alive after 12 months. The survivors demonstrated a significant decrease in functional autonomy and quality of life measured by EQ-5D[4] compared to their baseline (pre-illness) status ($p < 0.001$). Multivariate analysis shows a higher BI (≥60) and EQ-5D at hospital discharge is associated with full functional recovery ($p < 0.01$) at 12 months [40]. A prospective Israeli study of patients with greater functional dependency on admission, with 20% having a functional independence measure (FIM)[5] <60, had a 1 year survival of 22%. At this time point, only 11% of the original cohort had a FIM score ≥90, equating to living at home independently [28].

The patient's physical functional trajectory prior to admission impacts on both survival and the trajectory of physical recovery on discharge. Patients generally experience a stepwise deterioration in physical function on admission to ICU. This stepwise deterioration is greater than a matched hospital cohort. Ferrante et al modelled three physical function trajectories (minimal, mild-to-moderate and severe disability), before and after ICU admission in 281 individuals aged ≥70 years. They found the severity of disability increased over the year prior to admission in the mild-to-moderate and severe groups, but not in the minimal disability group. A quarter of those with minimal disability either died or became severely disabled. Forty percent with mild-to-moderate pre-ICU disability transitioned to severe disability and 25% died. Of those with severe pre-ICU disability, 33% experienced early death, while the survivors remained severely disabled [41].

To unpick the complex interaction of pre-admission functional levels with a number of other factors, Barnato et al [20] followed 26,072 Medicare beneficiaries; i.e. an aged population >70 years. Those who received mechanical ventilation were more likely to have worse baseline mobility, activity of daily living (ADL) disability scores and cognitive function. However, their prior functional status alone could not explain the increase in disability beyond that seen in survivors of hospitalisation alone.

[3]The Barthel Index (BI) is composed of 10 weighted items. The original score was marked out of 20; higher scores represent a greater degree of independence. Subsequent studies have sought to improve the sensitivity of the scale by extending it to 100 points.

[4]The EuroQol 5 dimensions (EQ-5D), comprises of five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. There are five levels under each domain.

[5]The Functional Independence measure (FIM) includes 18 items, 5 measure cognition and 13 are physical domains based on the Barthel Index. Each item is scored from 1 to 7 and is based on the level of independence, (1 represents total dependence and 7 complete independence). Possible scores range from 18 to 126.

2.1.5 Psychological function

The psychological sequelae of an ICU admission can be broadly categorised as depression, anxiety, post-traumatic stress and cognitive dysfunction. All of these are strongly associated with negative perceptions of HRQOL [42–45]. Reports of the prevalence of these disorders in the literature are inconsistent; while these conditions do not occur in isolation there is a tendency to report them as isolated occurrences.

In a systematic review involving 1213 ARDS survivors enrolled in 10 studies [46], the median point prevalence of clinically significant depressive symptoms was 28% (range 8-57%) [42, 43, 47, 48]. The widely varying population characteristics and inconsistencies in the tools used to identify depression may account for some of this variation. The rate of post traumatic stress disorder (PTSD) was reported to be 21-44% [44, 45, 49, 50], with patients exhibiting avoidant behaviours and many reporting intrusive thoughts or hyper-arousal. While these symptoms can be a normal reaction to what is perceived as a life-threatening event, symptoms often persisted, interfering with normal life. In this particular group of patients, a 24% prevalence of psychiatrist-diagnosed symptoms was still present at 8 years.

The risk factors for psychological symptoms following critical illness are gradually becoming apparent. When risk factors are assessed in post-ALI/ARDS for PTSD and depressive symptoms, significant predictors include sedation, a longer duration of mechanical ventilation and a longer intensive care unit stay. To what extent psychiatric disorders are newly acquired or pre-exist is difficult to establish. Most studies tend to exclude patients with prior histories of psychiatric disorders, although this has not been done consistently. Unsurprisingly, a prior history of depression is a significant predictor of post-ICU depression [43].

2.1.6 Cognitive function

Current research suggests that neurocognitive impairments following critical illness are common, long-lasting and are associated with decreased daily function, quality of life and an inability to return to work. Girard et al found severe impairments in memory, attention and executive function in 62% of medical ICU patients at their discharge from hospital. This cognitive dysfunction persisted up to 12 months in over half of those affected. The duration of delirium was independently associated with poor cognitive outcomes [51]. In a sicker group of patients with ARDS, 74% had cognitive impairment at hospital discharge, reducing to 46% at 2 years following discharge [47]. At 2 years, memory was affected in 13%, verbal fluency in 16% and executive function in 49% [52].

In a group of 448 ICU survivors, 40% had global cognition scores at 3 months that were worse than those typically seen in patients with moderate traumatic brain injury. Twenty-six percent had scores 2 standard deviations (SD) below the population mean, equivalent to a diagnosis of mild Alzheimer's disease. The median score measured by the RBANS[6] global cognition score was approximately 1.5 SD below the age-adjusted population mean, similar to scores for patients with mild cognitive decline. When 382 of these patients were re-tested at 12 months, the median score was similar, with 34% equating to moderate traumatic brain injury and 24% having scores similar to individuals with mild Alzheimer's disease. The authors found that a longer duration of delirium was independently associated with worse global cognition and executive function at 3 and 12 months [53].

These poor neurocognitive outcomes can remain apparent years after the critical illness. A German retrospective cohort study of 46 ARDS survivors found that 25% had poor cognitive function in various tasks assessing attention skills at 6 years following ICU treatment. Physical disability was found in 41.3% of patients. All ARDS survivors with cognitive deficits were disabled, with only 22.9% of the non-cognitively impaired subset having a physical function problem [54].

2.1.7 Impact on caregivers

Many papers have been published regarding the devastating impact of survivorship experienced by patients. However, the impact on families and carers can also be life-changing. Cox et al provided a distressing narrative of the strain experienced by the caregivers of 23 ARDS survivors at 3-9 months following hospital discharge.

> *"Once we were out of the hospital, we were on our own. Nobody realises that leaving the hospital is not the end for some people. The next place is just as hard, sometimes worse."* [55]

Symptoms of depression have been increasingly reported by many caregivers. The caregivers of 290 patients ventilated for >3 days were followed up by Douglas et al [56] 2 months after hospital discharge. Twenty-five percent of the caregivers were classified as depressed 16.7% of whom were deemed moderately or severely depressed. Informal caregivers of patients with depressive symptoms, and those caring for patients who experience the most lifestyle changes (for example, patients who did not return home) were affected the most [57–60]. The highest risk of depression was seen in carers of patients who were institutionalised following discharge

[6]RBANS, the Repeatable Battery for the Assessment of Neuropsychological Status, is a neuropsychological test. It consists of two tests for each of the five domains tested; immediate memory, visuospatial/constructional, language, attention and delayed memory.

[56]. The negative impact on caregivers' health outcomes can still be present at 2 years following discharge [60].

2.1.8 Impact on society

Following hospital discharge, patients recovering from critical illness continue to consume health care resources, primarily through rehabilitation services and accessing general practice. The use of such resources is dependent on the demographic of the population studied.

A majority of ICU survivors either do not return to their own homes or do so with increased support. Of a cohort of 92 Canadian ARDS survivors, 50% used home-care services in the first 2 years following discharge [61]. In 103 North American survivors of PMV, only 5% returned home without paid home healthcare. The remaining 95% were discharged either home with paid home healthcare (11%), to a long-term acute care facility (29%) or a skilled nursing facility (13%), or to a rehabilitation facility (18%) [29]. In a multi-centre, questionnaire-based study of survivors of critical illness in the UK, 25% reported that they required care assistance at 6 months and 22% at 12 months. The majority of this care was provided by family members (80% at 6 months and 78% at 12 months post-discharge) [58].

Subsequent readmission to hospital is also common for ICU survivors. Forty percent of Cheung's ARDS cohort were readmitted to hospital, half of whom were readmitted multiple times [61]. In another study there were 150 readmissions for 68 (67%) of the 103 PMV hospital survivors [29].

The largest portion of the total health care bill assigned to ARDS survivors is the initial hospital admission, with ICU costs accounting for 76% of the hospital tariff. Following discharge, subsequent hospitalisation and inpatient rehabilitation are the predominant costs followed by home-care, outpatient pharmacy and physician costs, with nursing being the largest part of the home-care costs [61].

Physical and to a greater extent, cognitive disabilities frequently prevent ICU survivors returning to work. A German 6 year follow-up study in 2001 reported on 46 ARDS survivors. Forty-five percent returned to work, however none of the 23% with cognitive impairments were able to return to work [54]. Fewer than 10% of patients who had received PMV and who had been previously employed returned to work by 2 years [29]. Similar statistics are reported by other authors [18, 47, 62]. Additionally, a 15% reduction in employment among informal caregivers of critical illness survivors has been described [63].

2.1.9 Relationship between physical and psychological function

"Orandum est, ut sit mens sana in corpore sano".

A sound mind in a sound body is to be prayed for. (Juvenal, 1st Century)

There has long been an implicit link between mental and physical health. The inter-dependency between physical and psychological function during and following critical illness is complex and poorly understood. Poor physical function in ICU survivors is a significant predictor of depressive symptoms in the first year post-ICU [43, 64]. Poor physical function on admission to ICU is also a risk factor for developing depressive symptoms [23]. Additionally, prior depressive symptoms are a strong independent risk factor for developing new physical impairments following ICU admission [23].

2.2 Theoretical frameworks for deterioration in physical function following critical illness

There is no clear framework to describe the mechanisms of injury that result in the poor physical function outcomes described in the previous section. Only recently has an attempt been made to determine a theoretical framework for functional dependence following critical illness [26]. This group has taken a translational approach, pairing clinical phenotypes with molecular mechanisms of injury in an attempt to derive a strategy to drive forward current research that has become bogged down in study population heterogeneity.

Greater interest is now being paid to the International Classification of Functioning, Disability and Health (ICF) [65]. This framework was developed and endorsed in 2001 by the 54^{th} World Health Assembly as a means of classifying health-related states at both an individual and population level. It is the frame of reference underpinning rehabilitation medicine, categorising acute illness and the subsequent sequelae, into:

- damage to body structures or "impairments" e.g. muscle weakness, fatigue, poor concentration,
- limitations to activities e.g inability to stand, poor exercise tolerance, inability to sequence getting dressed, and
- restrictions in participation in social roles, e.g. inability to return to work, to shop, to manage in own home.

This is a particularly useful framework for both developing interventions and for measuring outcomes from rehabilitation interventions in complex patient groups. It focuses clinicians' attention on impairments that require addressing to gain the desired functional outcome. For example, muscle weakness is the usual suspect in poor physical function outcomes; most interventions are therefore based around prevention of muscle loss or restoration of muscle function. However, it is not the only impairment that contributes to the disability arising from a deterioration in physical function. The received wisdom is that any observed recovery is simply the reversal of the injury sustained. However, the recovery of function and improvements in the disability experienced by patients may be a functional adaptation to a constellation of impairments.

The following section explores impairments that may be, or are accepted as being, ultimately responsible for functional disability. I then consider potential modifiers of the impairments themselves and of the related physical disability.

2.2.1 ICU-acquired weakness

ICU-acquired weakness (ICUAW), i.e. dysfunction of the motor unit, which consists of peripheral nerve, neuro-muscular junction and skeletal muscle fibre, is often cited as the cornerstone of functional problems following an ICU admission [32]. This label is habitually given to clinically weak ICU patients in whom there is no satisfactory explanation for their weakness other than critical illness. Depending on the diagnostic criteria and the duration of mechanical ventilation, the prevalence of ICUAW is reported as 25-100% [66–69]. At a cellular level three commonly described characteristics in patients with ICUAW have been found: selective thick filament loss, type II muscle fibre atrophy and muscle membrane inexcitability.

The association between muscular weakness and function has long been assumed. However, only recently has a clear association been demonstrated between muscle weakness and a reduction in physical function. Fan et al [69] assessed muscle and physical function and HRQOL in 222 survivors of acute lung injury. One third were discharged from the hospital with objective evidence of ICUAW which persisted at 12 months. This muscle weakness was associated with substantial impairments in physical function and HRQOL that were still evident at 24 months.

Critical illness myopathy (CIM) and polyneuropathy are widely recognised as the underlying culprits of ICUAW. The diagnostic criteria of both are well described in the literature [39] but a unifying molecular or cellular mechanism to explain their development, progression and/or recovery is still lacking. Both processes are often present in an individual patient.

However, there is no consensus as to the relative contribution of either to the global picture of ICUAW.

2.2.1.1 Critical illness myopathy

Critical illness myopathy is a primary myopathy, i.e. it is not secondary to muscle denervation. Recently, Poulson et al [70] found no differences in maximum electromyography (EMG) amplitude, EMG onset, reaction time or co-activation of either endurance or fast contractions, between ICU survivors and controls. This indicates an intact central motor drive, processing of visual information, signalling pathways from motor cortex to muscle and muscle activation strategy. They concluded that in light of the reduced rate of force development and a trend towards electromechanical delay, the deficits responsible for physical impairment in ICU survivors are most likely to be within the muscle tissue. Similarly, Angel et al [71], in a small cohort of patients, reported structural abnormalities in muscle biopsies in the absence of electrophysiological abnormalities. In contrast, Semmler et al [72] found no critical illness myopathy in any of the 51 post-ICU patients they investigated with EMG and nerve conduction studies at 6-24 months' post-discharge from ICU.

Histology findings are also extremely variable. In one study [73] of 98 muscle biopsies taken from 57 ICU patients, with the initial biopsy taken at 1-25 days after ICU admission, 38% were histologically normal, 31% demonstrated atrophy of both type 1 and 2 fibres and 31% showed necrosis. Fifteen patients had sequential biopsies, of which 69% demonstrated relative atrophy of the muscle fibres in the second sample while electron microscopy showed loss of myosin filaments.

Puthucheary and colleagues [74] have begun to explore the question of the relative contributions of decreased synthesis and increased degradation to the loss of muscle mass. They evaluated rectus femoris cross sectional area (CSA) on days 1,7 and 10 of ICU admission and took sequential muscle biopsies on day 1 and 7. A subgroup were also given before-and-after primed infusions of 1,2-$^{13}C_2$ leucine. In 28 patients assessed by all three measurement methods, on days 1 and 7, the rectus femoris CSA decreased by 10.3% (95% CI, 6.1-14.5%), fibre CSA decreased by 17.5% (95% CI, 5.8-29.3%) and the ratio of protein to DNA by 29.5% (95% CI, 13.4-45.6%). In those patients who had sequential muscle biopsies, myofibre necrosis occurred in 20 of 37 patients (54.1%). The pattern of intracellular signalling supported both increased breakdown ($n = 9$, $r = -0.83$, $p = 0.005$) and decreased synthesis ($n = 9$, $r = -0.69$, $p = 0.04$).

While ICUAW is typically associated with muscle wasting, muscle wasting does not always result in neuro-muscular dysfunction. Muscle strength, defined as the force per CSA, is dependent on the force generating capacity of a given amount of muscle and the total muscle mass available. Fundamentally, force per CSA and regulation of total muscle mass are modulated by different mechanisms and can both independently alter muscle strength. For example, in a model of prolonged nutritional deprivation, diaphragm mass was reduced by 50%, but diaphragm-specific force generation was normal [75]. Additionally, after 48 hours of mechanical ventilation, Le Bourdelles et al [76] showed limb muscle mass was reduced significantly without an associated reduction in muscle-specific force generation.

Conversely, it does not hold that enhancing or preserving muscle mass improves muscle-specific force generation. This was demonstrated in a study assessing muscle contractile performance in myostatin-knockout mice [77]. Myostatin is a negative regulator of muscle mass. While the force generating capacity of the knockout mice was greater, the specific force-generating capacity was much reduced. Furthermore, passive mechanical loading, applied for 2.5 hours, four times per day for 9 ± 1 days in immobilised, sedated and mechanically ventilated ICU patients prevented a 35% reduction in *ex vivo* muscle fibre function, despite similar reductions in muscle mass [78].

2.2.1.2 Critical illness polyneuropathy

Critical illness polyneuropathy (CIP) is a distal axonal sensory and/or motor polyneuropathy affecting both limb and respiratory muscles [79]. Proximal muscle groups are more affected than distal groups and facial motor control is spared [45]. A contemporary theory is that CIP is integral to the underlying process leading to multi organ-dysfunction.

Despite electrophysiological evidence of reduced amplitude of compound muscle action potentials and sensory nerve action potentials, with normal or mildly reduced nerve conduction velocities on around day 15 of ICU admission, there is little evidence to support structural changes to nerves in the early stages of CIP [79, 80]. However, electrophysiological changes can be evident within hours of the onset of critical illness [81]. In an animal model these changes recover relatively quickly [82].

One postulated mechanism for CIP is an impairment of the blood-nerve barrier (BNB) [83] due to accumulation of metabolites which is a result of hypoperfusion secondary to microvascular alterations in nerve capillaries. This results in axonal depolarisation. This process may be the result of mediators such as TNFα, serotonin and histamine released during a systemic

inflammatory response (SIRS) [79], although CIP occurs in the absence of an identifiable circulating mediator or neurotoxin [84]. An alternate hypothesis is that neurotoxic factors may disrupt the BNB [85]. The pathophysiology underlying the CIP that persists beyond 12 months remains elusive. Risk factors for the development of long-term critical illness neuropathy include the duration of ICU treatment, duration of ventilator support and a high Acute Physiology and Chronic Health Evaluation II (APACHE II) score but, interestingly, not a diagnosis of sepsis [72].

ICUAW clearly plays a major role in physical function deficits following critical illness. However, as demonstrated in the next section, muscle wasting occurs for many reasons other than sepsis. Prolonged bed rest, fasting, cardiac failure, adrenal dysfunction and malignancy are all states that frequently accompany sepsis.

2.2.2 Deconditioning as a result of bed rest

The negative impact of bed rest has been known as far back as Hippocrates [86]. Notwithstanding the impact of sepsis on skeletal and cardiac myocytes, bed rest itself has a profound effect on cardiac and skeletal muscle performance.

2.2.2.1 Skeletal muscle unloading

Duration of bed rest is the risk factor most consistently associated with muscle weakness throughout ICU follow-up. Muscle strength is 3-11% lower for every additional day of ICU bed rest after adjusting for all other risk factors [69]. Actual or simulated anti-gravity situations that mechanically unload muscle reduced muscle CSA by 6-24% in 8-197 days; the longer the duration the greater the loss of CSA [87]. Morphologically, there was a decrease in CSA of muscle fibres and a reduction in whole muscle volume and mass, but no change in the number of fibres [88]. There are considerable regional differences in the loss of CSA following bed rest [89]. There is also a shift in the contractile nature of the fibres toward fast glycolytic phenotypes [90]. For example, soleus, a postural muscle, is predominantly slow twitch and as such, is highly susceptible to disuse and fibre-type switching [91].

2.2.2.2 Cardiovascular deconditioning

The duration of inactivity and an individual's baseline cardiovascular fitness are the main determinants of the reduction in maximal aerobic capacity caused by bed rest [92]. In healthy individuals bed rest reduces peak $\dot{V}O_2$[7] by approximately 0.9% per day over 30 days, in-

[7] $\dot{V}O_2$ peak, the peak oxygen uptake or the peak volume of oxygen that can be utilised in one minute, during maximal or exhaustive exercise. It is measured as millilitres of oxygen used in one minute per kilogram of body weight.

dependent of age and gender, with a greater proportional loss of performance observed in fitter individuals. For example, five US college students were shown to decrease their peak $\dot{V}O_2$ by 27% following 18 days of bed rest [93]. After 10 days of bed rest 12 sedentary men showed 15% decreases in peak $\dot{V}O_2$. Shibata's ultra fit group, despite a protocol to normalise cardiac filling volumes, lost 20% of their peak $\dot{V}O_2$ in 18 days. This reduction in $\dot{V}O_2$ peak was concurrent with a 25% reduction in maximal cardiac output over the same time period [93].

Both resting and maximal heart rates are elevated following bed rest. While a reduction in vagal tone is the most likely explanation for the increase in resting heart rate, the mechanism for the elevated exercise heart rate remains unclear. However, it is likely to be a result of increased sympathetic tone.

Simulation of microgravity situations by head-down tilt have suggested that the reduction in stroke volume, approximately 12% over 2 weeks [94], is partly responsible for the reduced cardiac output. However, the relative contributions of a reduction in plasma volume (15% over 2 weeks) [94] and ventricular remodelling on ejection fraction and left ventricular end-diastolic volume (-20% over 2 weeks) [94] is unclear. In healthy individuals, it is possible to attenuate these effects by regular supine exercise, but only in the presence of volume loading. This suggests that both volume depletion and cardiac atrophy are independently responsible for the reduction seen in stroke volume [95].

While muscle weakness is the oft-cited and investigated impairment, critically ill patients are also subject to severe cardiovascular deconditioning [96, 97]. Therefore, due consideration needs to be given to the cardiovascular stress that rehabilitation interventions are imposing on patients. If patients have been in ICU for protracted periods of time with little or no physical activity, commencing rehabilitation will potentially bring some very close to their maximum exercise capacity. Extrapolating from studies in healthy individuals, a patient receiving PMV in the ICU, whose peak exercise capacity was reached by walking at 3 mph pre-illness (3.3 METs[8], roughly 11.5 $mL.Kg.^{-1}min^{-1}$), who is on bed rest for 30 days, even without sepsis, will see a reduction in their peak exercise capacity to only being able to walk at 2 mph (2.5 METs, 8.75 $mL.Kg.^{-1}min^{-1}$). This does not allow a great deal of scope for rehabilitation. Indeed, this evidence is inline with recent data from the Manchester Royal Infirmary where patients ventilated for $\geq$14 days had significantly lower peak $\dot{V}O_2$ than those ventilated for 5-14 (12.9 $\pm$ 3.7 vs. 15.3 $\pm$ 4.2 $mL.Kg.^{-1}min^{-1}$, $p = 0.023$) [97].

[8] 1 MET or metabolic equivalent = 3.5 $mL.Kg.^{-1}min^{-1}$

2.2.2.3 Disuse skeletal muscle atrophy

Disuse is a major determinant of the skeletal muscle phenotype. The evidence regarding the relative contribution of muscle protein synthesis and muscle protein breakdown in human skeletal muscle, as a result of disuse, is currently favouring a reduction in muscle protein synthesis [98]. However, there are also profound alterations in muscle metabolic performance as a result of disuse. Not only is there a marked change from oxidative to glycolytic metabolism, but there is also a significant down-regulation of the transcriptional co-activator, PGC1-α [99].

2.2.3 Sepsis-induced myocardial dysfunction

In addition to the effect of bed rest on myocardial function, sepsis also alters cardiac performance. A reduced ejection fraction is seen in 50-64% of patients with sepsis [100, 101] and in non-septic ICU patients up to 4 weeks following ICU admission [102]. Although not a major suspect in long-term functional disability, myocardial dysfunction during the early stages of rehabilitation is an important consideration when prescribing an exercise intensity for a rehabilitation program.

2.2.4 Bio-energetic failure

Mitochondria are the main producers of the cellular energy substrate ATP required for cardiac and skeletal muscle function. Mitochondrial dysfunction occurs in critically ill patients and is associated with non-survival from ICU [103]. Fredriksson et al demonstrated a 2-fold decrease in the mitochondrial content in both vastus lateralis and intercostal muscle of a small group of ICU patients with multi-organ dysfunction, 2-22 days after admission, compared to healthy, age and sex-matched, patients undergoing surgery [104]. They also found that the activity of mitochondrial complex IV, the last part of the electron transport chain, was 30% lower in vastus lateralis than in the intercostals and this was accompanied by a 40% increase in serum lactate. This finding led the group to postulate that mechanical stretching of the respiratory muscle during mechanical ventilation may play a role in the preservation of mitochondrial function. More recently, Mofarrahi et al demonstrated that the locomotor muscles of septic mice were more susceptible to sepsis-induced mitochondrial injury and autophagy than respiratory muscles [105]. Furthermore, stimulation of mitochondrial biogenesis, the production of new mitochondrial proteins and apparatus, at day 1-2, is associated with ICU survival [106].

2.2.5 Neurocognitive deterioration

Outside critical care there is a fast-growing body of literature suggesting that exercise may attenuate cognitive impairment and reduce dementia risk [107]. Mechanisms by which this occurs are unclear, but most probably occurring through;

i) neurogenesis in the hippocampus, resulting in improved memory and learning [108],

ii) neurotrophic factors such as BDNF, IGF-I, synapsin-I and ghrelin which increase during (or as a result of) exercise, and may be responsible for maintaining not only the health of existing pathways but stimulating the growth and differentiation of new neurones [109], or

iii) increased angiogenesis [110].

However, based on a rat model, exercise within 2 weeks of brain injury may decrease BDNF and impair learning, therefore the timing of exercise may be crucial [111, 112]. Neuroendocrine or inflammatory mechanisms triggered by depression may affect physical function [113]. However, behavioural factors may also be responsible. For example, patients with depression are difficult to engage in rehabilitation. It is also likely that depressive symptoms influence a patient's perception of what they are able to do when they are followed up.

2.2.6 Modifiers of impairments and limitations to activities

While increasing age, a greater burden of co-morbid illness and prolonged ICU stay as a direct consequence of the admission illness are difficult factors to change [114], impairments such as ICUAW, cardiovascular deconditioning and cognitive and psychological function are all, individually, potentially modifiable through various rehabilitation interventions. However, the underlying therapeutic mechanisms for the benefits of exercise/rehabilitation in these patients requires further delineation.

Exercise improves skeletal muscle performance in both health and disease [115] and is typically divided into endurance and heavy resistance, creating markedly different phenotypes. It is accepted that endurance training stimulates:

- mitochondrial biogenesis,
- fast-to-slow twitch fibre type transition,
- change in substrate utilisation, favouring fatty acid over glucose metabolism,
- angiogenesis.

Heavy resistance training stimulates the synthesis of the contractile proteins responsible for muscle hypertrophy and an increase in maximum force output. Endurance training in athletes [116] and heart failure patients [117] is associated with up-regulation of mitochondrial biogenesis, as measured by markers of biogenesis, such as the transcriptional activation factor PGC1-α in skeletal muscle tissue. PGC1-α also has other important roles in the regulation of

fibre-type transition during bed rest and exercise which may be of importance during critical illness. For example, there tends to be greater loss of type I fibres than type II[9] following bed rest and sepsis. Interestingly, this type I to type II fibre-type transition is often considered partly responsible for the reduced excise capacity seen in patients with chronic obstructive pulmonary disease (COPD) and chronic heart failure [118]. Conversely, exercise stimulates a transition from type II to type I and is associated with an increase in PGC1-α. Similar up-regulation in patients recovering from critical illness may translate to improved exercise capacity and hence, improved functional outcomes.

Age-related muscle atrophy may play a significant role in elderly patients' ability to recover from ICUAW. Younger patients, who have been exposed to less sarcopenia before the onset of critical illness, may have more capacity to compensate for ICUAW. This may also be important with comorbidities such as COPD, chronic heart disease (CHD) and chronic kidney disease (CKD) all of which have significant effects on muscle function even before ICU admission.

Rehabilitation is a modifier of physical function, enabling patients to develop coping strategies to manage their impairment level problems. Given that muscle strength recovers before physical function and HRQOL [69], persistence of physical function limitations are likely to be due to a combination of factors. These factors include, but are not limited to, cognitive and mental health morbidity [23], home environment and caregiver support [56, 60]. How ICUAW is modulated by such factors is as yet unclear [26]. However, a patient's mental health, along with the extent to which their caregivers are supported, as well as other environmental factors will greatly influence how a patient's physical dependency affects their role in society.

While many interventional studies have demonstrated that rehabilitation is possible for a significant proportion of patients [119–121], "rehabilitation" remains a complex entity. One which is dependent on a number of interacting factors including, but not limited to, health care culture, staffing, patient delirium and severity of illness. Ultimately, a complex intervention that encompasses both the physical and psychological aspects of recovery is most likely to be effective. However, as I will demonstrate in the next section, very little is known about the individual aspects of providing a rehabilitation intervention.

[9]Type I or "slow twitch" fibres, (referring to the Myosin Heavy chain ATPase activity) are predominantly aerobic muscle; they are less fatiguable than Type II or "fast twitch" fibres (IIa and IIx) which are predominantly glycolytic.

2.3 Interpretation of current published work

There has been an exponential increase in the number of publications regarding rehabilitation or "early exercise" in critical care (*Figure 2.1*). However, there are very few interventional studies and interpretation of those that have been published is complicated by the lack of an explicit theoretical framework. The type and dose of any intervention and the stage and severity of the patient's illness may be crucial factors in the impact of a rehabilitation program. With this in mind, I shall review the current literature base with respect to those studies providing sufficient information with regarding the timing of the intervention, the intervention itself, and the severity of illness of the enrolled patients (Tables 2.1 and 2.2).

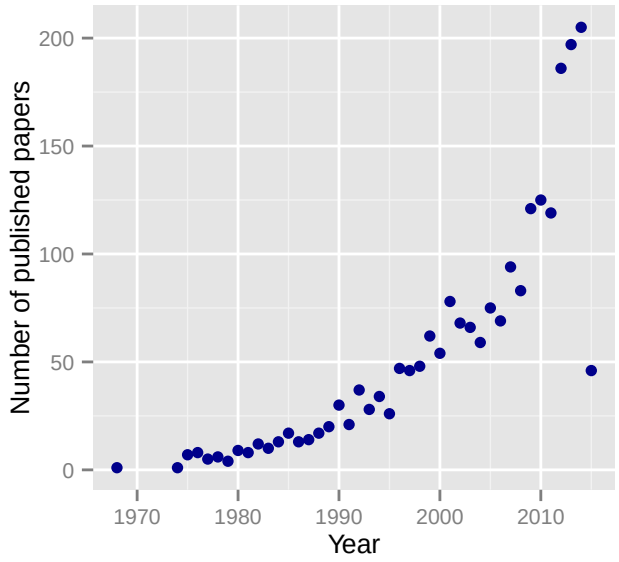

Figure 2.1: ICU-related rehabilitation papers on PubMed 1968 to 2015.
(Data downloaded March 2015)

2.3.1 Timing

A fundamental issue that continues to be avoided in study design is whether the intervention is:

i) targeted at an impairment level i.e. limiting, or even preventing, the detrimental effects of bed rest and/or sepsis-induced nerve, muscle and cardiac injury,

ii) an impairment-level intervention promoting recovery, or

iii) an impairment and limitation-level rehabilitation program, focusing on patient-specific impairments (e.g. muscle weakness or cardiovascular deconditioning) in order to facilitate maximum independence.

Muscle injury occurs early in the ICU admission [122]. Thus, the correct timing of the correct intervention may be crucial. One could argue that the earlier the intervention, the more impact it will have on prevention of the detrimental effects of bed rest and sepsis. In later interventions, the mechanism is most probably promotion of recovery. The current European guidelines, based on expert opinion rather than evidence, recommend starting when the patient is "medically stable" [123]. Indeed, this has been common practice in most London teaching hospitals since the early 2000's (personal communications).

There are currently seven studies, four of which are randomised controlled trials (RCT), of interventions that intended to commence before day 5 of an ICU admission [119, 120, 124–128]. Eight studies commenced after day 5, four of which are RCTs [121, 129–135]. However, while the studies enrol patients at this time-point, few are explicit about when different aspects of the intervention actually start. As such, some patients may have only received passive mobilisation on day 1 and not have experienced active rehabilitation e.g. sat over the edge of the bed (SOEB), until day 14.

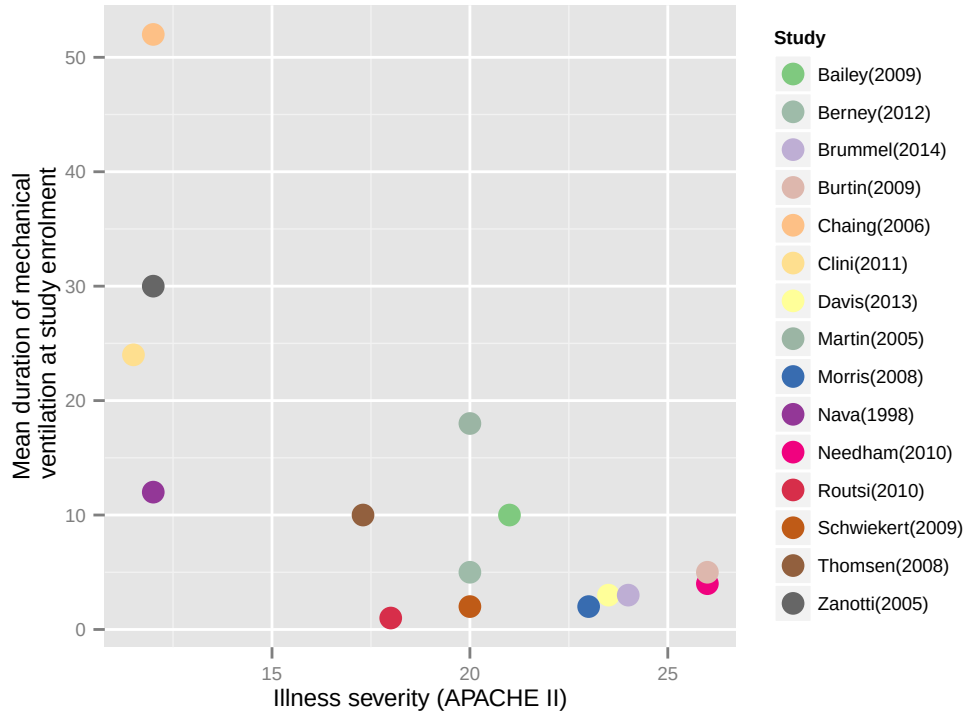

Figure 2.2: Interventional Rehabilitation Studies. Illness severity vs. mean duration of mechanical ventilation at study enrolment. APACHE II (Acute Physiology and Chronic Health Evaluation II).

2.3.1.1 Interventions before day five

Three studies started within 72 hours of ICU admission [119, 124, 125]. The most prominent of these studies, by Kress' group in Chicago [119], assessed the effect of combining daily inter-

ruption of sedation with physical and occupational therapy on functional outcomes in patients receiving mechanical ventilation in intensive care. They randomised ICU patients mechanically ventilated for <72 hours who were functionally independent prior to admission, to either mobilisation (physical and occupational therapy) during periods of daily interruption of sedation (n = 49) or to daily interruption of sedation with therapy as ordered by the primary team (n = 55). The time to first-out-of-bed in the intervention group was a median of 1.7 days (interquartile range (IQR) 1.1-3.0) vs. 6·6 (IQR 4·2–8·3) in the control group. Twenty-nine (59%) patients in the intervention group returned to independent functional status at hospital discharge, compared with 19 (35%) control patients. The difference between groups did not appear until after ICU discharge, leading to a number of questions: does exercise in ICU precondition patients to cope with further rehabilitation, or does it prevent a decline in function, providing an improved baseline for further rehabilitation? However, while this group mobilised early, they had a much lower APACHE II score (18) and average age (55 years) compared to patients in other early intervention studies.

Routsi et al [124] instigated daily electrical muscle stimulation (EMS) within two days of ICU admission in 104 ICU patients. They finally evaluated 52 patients, following considerable dropout. Using an MRC sum score[10] cut-off of 48/60 to diagnose critical illness polyneuro-myopathy (CIPNM), they reported a significantly lower incidence of CIPNM in the intervention group, 3 compared to 11 patients in the control group, (hlOdds Ratio (OR) = 0.22; CI: 0.05-0.92, p = 0.04). No functional data were available. However, there was no intention to treat analysis and all patients receiving paralysing agents in the intervention group were excluded from analysis. It is also unclear what baseline rehabilitation was received.

Davis et al [125] carried out a small (n = 15) prospective cohort study in a targeted, aged population ≥65 years. They had received mechanical ventilation >72 hours, with a pre-admission Barthel Index score ≥70. These patients were recruited early, were elderly (mean age 76 years) and had a mean APACHE II of 23.5 (above the average of the 14 studies reviewed). However, only 41 (24%) of the mobilisation sessions involved intubated patients. They did not give information regarding time to first SOEB.

Most recently, Brummel and colleagues investigated the feasibility of a combined cognitive and physical therapy intervention [126]. They randomised 87 medical and surgical ICU patients to usual care (UC), early once-daily physical therapy (PT), or an early once-daily physical therapy plus twice-daily cognitive therapy (CT) protocol, within 72 hours of admis-

[10]MRC sum score measures 6 antigravity muscle groups, wrist, elbow, shoulder, hip, knee and ankle flexion using the 1-5 MRC muscle grading scale, giving a total possible value of 60.

sion. The CT included orientation, memory, attention and problem-solving exercises. The PT included progressive mobilisation. Both intervention groups performed SOEB on day 1 or 2 after enrolment. This study recruited a relatively sick group of patients (mean APACHE II = 24), and mobilised them early *(Figure 2.2)*. In the CT and PT groups, 95% received CT every day, with 98% receiving PT on 75% of the days. Of the PT group, 95% received PT on 67% of the days. In the UC group, 77% received PT on 17% of the days. Cognitive, functional and health-related quality of life outcomes did not differ between groups at 3 month follow-up. However, the study was not powered to find a statistically significant difference between groups for either the cognitive test battery, functional outcomes of TUG[11], Katz[12], or Functional Ambulatory Category (FAC)[13]. While feasibility was demonstrated, 17% of the CT and PT groups dropped out. The severity of illness in the control group (mean APACHE II = 27), was greater than either of the intervention groups (PT = 21, PT and CT = 25).

Morris et al [120] prospectively assessed the impact of a daily mobility protocol on patients in a medical ICU in North Carolina. All medical admissions were enrolled within 48 hours of intubation and 72 hours of admission. Over a two year period 330 (23%) of 1427 intubated admissions met the study criteria. Of these, a third were receiving vasopressors. In the UC group 47.4% underwent at least one physical therapy session compared with 80% of protocol patients ($p < 0.001$). Of 64 UC patients who received PT, 12.5% had PT initiated during ICU treatment compared with 91.4% of protocol patients ($p < 0.001$). However, only 18 (10.9%) of these patients got as far as SOEB. After adjusting for BMI, APACHE II and vasopressor usage, UC patients were first out of bed in 11.3 days compared to 5 days for protocol patients ($p < 0.001$). This shows an unsurprising association between implementation of a mobility protocol and time to first out of bed. In the USA, at the time of publication, this was considered early rehabilitation in a relatively sick group of patients. However, it probably reflected current practice in London teaching hospitals at the time (personal communications).

Needham et al [127] carried out a quality improvement project, comparing outcomes before and after employing full-time physical and occupational therapists, and a multidisciplinary team commitment reducing sedation. The intervention group comprised 57 patients who had received mechanical ventilation >4 days. The patients were relatively young compared to the other studies, (mean age 50 years). Benzodiazepine use decreased markedly following the intervention and patients had improved sedation and delirium status. There were more rehab-

[11]TUG; is the time taken for a patient to rise from a chair, walk 3 m at a comfortable and safe pace, turn and walk back to the chair and sit down. Originally designed for elderly patients, to assess their risk of falls.

[12]Katz is a 6 item Activity of Daily Living scale. The items, Bathing Dressing, toileting, transferring, continence and feeding are graded as to dependent = 0, independent = 1, scored out of 6.

[13]FAC categorises patients according to basic motor skills necessary for functional ambulation. There are 7 levels. 1 = Non functional, 7 = Independent on level and non-level surfaces [136]

ilitation treatments per patient (median 1 vs. 7, p <0.001) and a higher proportion of those treatments involved sitting (or greater mobility) (56% vs. 78%, p = 0.03). However, they did not report the time to first SOEB.

Burtin et al [128] compared standard physiotherapy with standard physiotherapy plus cycle ergometry in 90 patients with an expected length of stay >7 days. They recruited one of the sickest groups of patients with a mean APACHE II score of 26.5, however the intervention group did not start exercise until day 14 *(Figure 2.2)*. The standard physiotherapy group received active or passive motion of upper and lower limbs, with intensity increased according to the individual patient's capabilities. Ambulation was started when it was considered appropriate by medical staff. The treatment group had active or passive training sessions of 20 minutes using a bedside ergometer five times per week, with sedated patients cycling passively. When patients were able to cycle actively, this was done in two bouts of 10 minutes, with intensity increased as tolerated. 6MWD at hospital discharge, the primary outcome, was greater in treatment compared with control patients (196 m (126-329 m) vs. 143 m (37-226 m)). However, actual vs. predicted 6MWD was severely reduced for both groups at 29% (19-43%) and 25% (8-36%) for control and intervention groups, respectively. There was a greater relative increase in quadriceps force between ICU discharge and hospital discharge in the treatment group (1.83 ± 0.91 to 2.37 ± 0.62 $N.Kg^{-1}$, p <0.01) than in controls (1.86 ± 0.78 $N.Kg^{-1}$ to 2.03 ± 0.75 $N.Kg^{-1}$, p = 0.11). Despite no significant difference in quadriceps force between the two groups on ICU discharge. The physical functioning section of the SF-36 score was higher in the treatment group (mean (CI), 21 points (18-23) vs. 15 (14-23), p <0.01). The proportion of patients with a Berg Balance Scale[14],"sit to stand" score of ≥ 2, (indicating the ability to stand independently) did not differ between groups at ICU (34% vs. 23%, p = 0.40) and hospital discharge (85% vs. 79%, p $\geq$ 0.74). The proportion of patients with a FAC score ≥ 4[15] was also similar at ICU (10% vs. 14%, p = 0.72) and hospital discharge (73% vs. 55%, p = 0.18). Despite the similarity between groups on ICU discharge in both muscle strength and ability to stand or mobilise independently, the intervention group demonstrated improvements in HRQOL and 6MWD. The authors postulated that either passive movement [138] or better coordination [139] were factors that led to later improved outcomes. During the 2 year study period, only 90 patients were recruited, representing just 5.9% of ICU admissions.

[14]Berg balance scale, was designed to assess falls risk in elderly patients [137]. It has 14 items, scored from 0-4 each

[15]Indicating the ability to walk independently.

2.3.1.2 Interventions after day 5

There is little evidence to demarcate the phases of damage and recovery to nerve and muscle in the course of critical illness. Therefore, the cut-off of 5 days to divide these studies into restorative rather than preventative is arbitrary and pragmatic. However, the seven studies that recruited patients after day 5 represent more complex interventions performed in patients with lower illness severity.

Bailey et al [121] studied the feasibility and safety of early activity in 103 respiratory failure patients ventilated$\geq$ 4 days, 92 of whom were mechanically ventilated. The enrolled patients had been in another ICU for 10.5 $\pm$ 9.9 days. Once transferred to their respiratory ICU (RICU), they received twice daily physical therapy (PT) with the goal of ambulating$\geq$ 100 feet before ICU discharge. They performed 1,449 activity events in 103 patients. Activity events included 233 (16%) sitting on the edge of the bed, 454 (31%) sitting in a chair and 762 (53%) ambulation. Forty one percent of the activity events were in patients with endotracheal tubes, 249 (42%) of which were ambulation. Thirty-four patients went home, while 49 went to either rehabilitation or an extended care facility. Of those who survived to hospital discharge 2.4% had no activity on RICU discharge, 4.7% could sit on the edge of the bed, 15.3% could sit in a chair and 8.2% ambulated <100 feet and 70% of admissions could mobilise$\geq$ 100 feet. The median distance ambulated by hospital survivors was 200 feet (range 0-600).

Thomsen et al [129] investigated whether transfer of respiratory failure patients from a general ICU to an RICU improved ambulation independent of their underlying pathophysiology. They included 104 patients who had been in a previous ICU for >2 days and who had received mechanical ventilation for >4 days in their RICU. The patients were mobilised 10.3 $\pm$ 7.5 days after their initial ICU admission. Using multivariate logistic regression adjusting for co-variables, they found four significant predictors of increased ambulation: transfer to RICU ($p < 0.0001$), absence of sedatives ($p = 0.009$), female gender ($p = 0.019$) and lower APACHE II scores ($p = 0.017$). This supports their hypothesis that the general ICU philosophy of care and the environment was partly responsible for poor physical function outcomes. This highlights, health care culture as a significant factor in the decision to mobilise patients, rather than the patient's level of sickness.

Nava et al [130], who published the first prospective RCT in this area, studied the effect of a pulmonary rehabilitation (PR) program on 80 Italian COPD patients recovering from acute respiratory failure, 61 of whom were mechanically ventilated. They started their rehabilitation 5-19 days following their original ICU admission. The 60 PR group patients received passive

mobilisation, early ambulation, respiratory and skeletal muscle training and, if able, lower extremity treadmill training. The 20 control patients received standard therapy including an ambulation program. Functional ambulation was regained at hospital discharge in 87% of the PR group vs. 70% in the control group. At discharge, 6MWD results were significantly better in the PR group ($p < 0.001$) with a mean increase of 100 m vs. 50 m in the controls. Interestingly, hospital length of stay was longer in the intervention group. Of note, the control group received more rehabilitation than most patients currently receive in the UK.

Clini et al [132] prospectively evaluated, in 77 patients, the association between the degree of change in functional status after a daily rehabilitation regimen and the clinical outcomes of remaining ventilator-free and surviving. Rehabilitation began 24 ± 3 days following their ICU admission. The rehabilitation regimen included supported and unsupported limb exercise with an ergometer for a minimum of 15 sessions, plus functional rehabilitation. They measured the change in Katz score, survival and weaning success rate as their clinical outcomes. Sixty-seven (87%) of the 77 enrolled patients survived, 74% of whom were liberated from mechanical ventilation. There was a mean ± SD increase in Katz score of 2.5 ± 2 points. Better functional capacity was associated with the probability of remaining ventilator-free ($p = 0.043$) and of hospital survival ($p = 0.001$).

Zanotti et al [133] recruited 24 Italian COPD patients who had received mechanical ventilation >30 days. The control group received active limb mobilisation and the intervention group EMS 30 minutes twice a day for 28 days. Patients demonstrated a decrease in the number of days to transfer from bed to chair (10.75 ± 2.41 days vs. 14.33 ± 2.53 days, $p < 0.001$).

Martin et al [131] retrospectively evaluated the prevalence and magnitude of weakness in 49 patients who had received mechanical ventilation for 18 ± 7 days. Observations were made of muscle strength and functional status after a non-randomised "whole-body" rehabilitation program. On admission, all patients were bedridden and had severe weakness of upper and lower extremities measured by a 5-point muscle strength score. Following rehabilitation, patients demonstrated an increase in upper and lower extremity muscle strength: upper limb from 1.9 to 3.6, lower limb from 1.5 to 2.7 ($p < 0.001$). All were able to stand and 81% could ambulate by hospital discharge. This demonstrates the potential for significant changes in muscle strength and functional capacity over time, but not an association with rehabilitation interventions.

Chiang et al [134] examined the impact of 6 weeks' physical training on the functional status of 20 patients who required PMV. The cohort reflected an aged population with an average age similar to that of Davis et al [125]. However, the average duration of mechanical ventilation at enrolment was 4 times the average of the 14 studies. Physical training, performed 5 days per week included strengthening exercises for upper and lower limbs and functional activity training. The control group received nothing beyond encouragement from nursing and medical staff. Over the 6 week period, muscle strength increased significantly in the intervention group and deteriorated in the controls. However, the increased strength in the intervention group was insufficient to return them to their predicted pre-morbid levels. Physical function was assessed using FIM. The total FIM score decreased in controls but increased significantly in the intervention group. However, muscle power deteriorated in controls yet the motor component of their FIM score remained the same. Thus, FIM may be insufficiently sensitive to detect change at this low level of functioning, or that further deterioration in muscle power was insufficient to impact on the FIM score. Additionally, the small deterioration in total FIM score of the control group was generally due to deterioration in executive function, rather than any further decline in physical function. This perhaps highlights the role of cognitive function in the development of physical function limitations.

The only interventional study with follow-up to 12 months after ICU discharge was carried out in Melbourne, Australia [135]. This study recruited patients from days 5-11 of their ICU admission. Patients had a mean and IQR age of 60 (15.8) and a mean ± SD APACHE II of 20 ± 7.7. Only 55% of the patients were ventilated at the beginning of the study. They used an exercise prescription approach to create rehabilitation programs for 74 patients. The rehabilitation programs started in ICU and continued to the ward and then out into the community. While the trajectory of improvement in 6MWD and TUG was greater in the intervention group, there was no significant difference in any of their outcomes.

2.3.2 Safety

The primary concern for ICU clinicians, given the tenuous stability of some of their patients, is safety during rehabilitation. Indeed, Thomsen et al [129] found that for every point decrease in the APACHE II score, the likelihood of ambulation increased by 6%.

If the definition of safety is the absence of "critical events" e.g. cardiovascular compromise, falls or accidental extubation, the question of safety has been answered. Nydahl [140] reviewed 16 publications reporting safety data, where the focus of the rehabilitation was to mobilise patients onto the edge or out of bed. Using the inherent safety limits, the mean

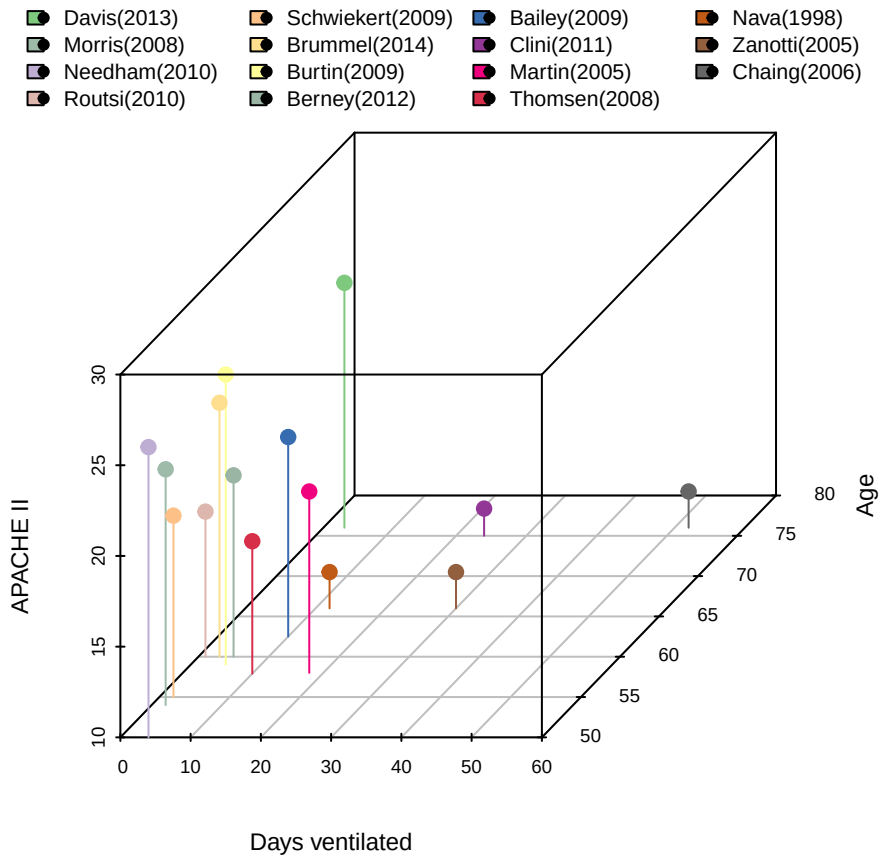

Figure 2.3: Rehabilitation studies by age, severity and days ventilated.

reported complication rate was 3 ± 9% (n = 144) in 453 patients and 3613 mobilisation episodes. Serious complications that led to further consequences were observed in 10 (3%) of cases.

Similar results were seen in a single-centre prospective evaluation of 1110 intensive care unit admissions with 5267 physical therapy sessions [141]. There were 34 (0.6%) adverse events. The majority 18 (53%) of which occurred when sitting patients on the edge of the bed. The authors did not provide information regarding the illness severity of the patients. A group in Brazil [142] recruited 19 patients within the first 72 hours of mechanical ventilation into an observational study involving 20 minutes of passive leg cycling using an electric cycle ergometer. This cohort had an average SOFA score of 6 ± 3. They reported only 2 minor adverse events, neither related to haemodynamic instability, although they do not report how many cycling episodes were carried out in total.

Consensus recommendations on the limits to start and continue rehabilitation have since been published [143]. Interestingly, the one area on which consensus was not gained was the concurrent use of inotropic or vasopressor support. The issue of patient capacity to respond safely to a physiological challenge beyond that they are already experiencing as a result of

their illness has yet to be considered. This is in part because there is no definitive way to evaluate subtle harm caused to sub-cohorts of patients. For example, the time to death of the non-survivors of Schweickerts' intervention group was significantly less than that of the control group (2.5 days (95% CI: 2.4-5.5) vs. 9.5 days (95% CI:5.9-14.1) p <0.04) [119]. Potentially coincidental, this is non-the-less, a warning that early exercise may not be beneficial in all patients.

2.3.3 Variations in baseline or usual care

Several challenges are inherent in the interpretation of these rehabilitation studies, particularly with respect to differences in the structure of care of mechanically ventilated patients across North America, Europe and Australia. North American ICUs manage critically ill patients with multi-organ failure during the acute phase of their illness, whereas patients with single organ failure requiring ongoing ventilatory support are managed in long-term Acute Care Units. This is in direct contrast to the UK where ICUs generally provide long-term ventilatory support for up to 6.3% of their mechanically ventilated admissions [144]. Of equal importance, European [145] and Australian [146] physiotherapists provide both rehabilitation and respiratory care to ICU patients, although the extent to which rehabilitation is delivered varies considerably [146–152]. In contrast, respiratory therapists provide respiratory care in North America, while physical therapists, the presence of whom is currently limited but not absent in ICUs [153], provide rehabilitation. To a certain extent this difference provides an opportunity to investigate the impact of early physical interventions against a control group [119, 134], unlike studies that originate from Europe or Australia, where interventions would be compared to a baseline of current clinical practice. Both of these situations impact on the "start point" of the interventions along the continuum of a patient's critical illness, the prior exposure of the patient to variable periods of non-intervention and to the baseline interventions that are common practice in some centres. Therefore, it is important to establish whether a training load has been delivered to all patients in the intervention limb of a study, and whether this is actually different to that delivered to the control group [154].

2.3.4 What is the intervention?

Rehabilitation in the context of critical care takes on many different forms. "Early mobilisation", a term used in North American studies, includes the application of traditional modes of physical therapy at an earlier stage than their conventional practice and is delivered more frequently. These interventions are often protocolised [155]. In contrast, "Enabling and supporting individuals to recover or adjust, to achieve their full potential and to live as full and active lives as possible" [156], is more of a European descriptor of rehabilitation.

Many of the programs that recruit patients early may only involve passive exercise in the early stages. Given that continuous passive movement use for 10 hours per day is required to prevent a reduction in *ex vivo* muscle fibre function [78, 138], it is not clear what role this aspect of the rehabilitation program takes in the preservation of muscle function, beyond maintaining joint range of movement. Traditionally, rehabilitation has been about enabling patients to regain functional autonomy. More recently in the context of critical care, it has become about breaking the cycle of bed rest. How this cycle is broken (e.g. tilt-tables, active arm and leg cycle ergometery or even interactive video games, [157]), may not be important. What may be important is the level of engagement of the patient in the activity. For example, EMS is an impairment level intervention and as such, it is unlikely to have the same psychological role as engaging a patient in a rehabilitation program. Also this will not provide patients with strategies to minimise their functional disability. Conversely, early mobility programs, whatever the intervention, may engage the patient and prevent some of the cardiovascular consequences of bed rest. However, one needs to be mindful of the myocardial depression endured by some patients during the early stages of their illness.

The common factor with all of these interventions is that we do not know how to measure the dose. The conceptual framework of both pulmonary and cardiac rehabilitation, and one that might be applicable to the rehabilitation of patients in critical care, is grounded in the concept that physical activity presents a serious challenge to homeostasis [158]. When patients are repeatedly exposed to, and have the capacity to respond appropriately to such a challenge, the inherent adaptations that follow are usually associated with improved physical performance. This is borne out by the well-established link between functional capacity and exercise capacity in the normal, cardiac and pulmonary rehabilitation populations. In other words, functional capacity is influenced by the individual's cardiovascular fitness i.e. their ability to take up, transport and utilise oxygen. One would expect all rehabilitation interventions, e.g. sitting upright in bed, sitting over the edge of the bed, transferring to a chair, or cycle ergometry, to increase a patient's energy consumption beyond their resting metabolic rate. However, these activities are currently described in terms of absolute exercise intensity and not one that is relative to the patient's current state of fitness. Hence, a fixed increased activity for one patient may be well within their current level of cardiovascular fitness, but for another patient it may impose significant physiological stress.

2.3.5 Measurement of outcome

Measurement of outcome from rehabilitation studies is inconsistent. In 14 studies 14 different outcome measures were used. There has been a recent call for future published work to provide a consistent minimal data set for post-ICU interventions and a consensus on outcome measurement [159].

2.3.6 Financial implications

Few authors have investigated the cost effectiveness of early rehabilitation programs. The Johns Hopkins Hospital Medical ICU [160] developed a cost model for North American ICUs with 200, 600, 900 and 2,000 annual admissions. The model accounted for both conservative and best-case reductions in ICU and hospital length of stay (LOS), based on their own data from implementing, removing, and then re-implementing a rehabilitation program on their ICU. Costs were based upon data published in 2008 [161]. Their example scenario of 900 annual admissions and length of stay reductions of 22% and 19% for the ICU and ward, respectively, gave a net cost saving of $817,836. They modelled 24 scenarios using 10% and 25% reductions for both ward and ICU LOS, varying the ICU and ward costs from 80-120% and with 200-2,000 annual admissions. The financial projections ranged from $87,611 (net cost per scenario) to $3,763,149 (net savings per scenario). Net savings were demonstrated with 20(83%) of the scenarios.

2.3.7 Summary

The underlying mechanisms which result in impairments leading to the physical function problems following ICU admission are still not fully elucidated. Several factors, caregiver support, cognitive and psychological function modulate how these impairments manifest as poor physical function outcomes. Some factors, while not open to modulation, age, pre existing disease and prior physical function deficits are major determinants of how an individual will respond to a rehabilitation program.

The age, severity of illness and the time point that patients are recruited into the few published interventional studies vary considerably, as does the type of intervention (*Figure 2.3*). This makes extrapolation into a clinical setting a serious challenge. Although there is a general trend towards increasing severity with decreasing time to enrolment in the studies (*Figure 2.2*), the 2 studies that commenced within the first 48 hours did not have the highest severity of illness. This is important to take into consideration as they may not reflect the severity of illness in UK ICU patients. Additionally, we do not know how to choose the correct dose or, indeed, what the intervention should be.

Over training, the symptoms of which include but are not limited to fatigue, insomnia and worsening physical and psychological performance, may seem an unusual concept in an ICU patient. Indeed these maybe potentially impossible to separate from the consequences of an ICU admission. However, if patients are exposed to cardiovascular deconditioning as much as the literature suggests, then there is the potential to overstretch if not "over train" patients. The limited available evidence suggests that active rehabilitation interventions, e.g. sitting on the edge of the bed, standing, transferring to a chair or cycle ergometry, increase a patient's energy expenditure beyond their resting metabolic rate, therefore presenting a homoeostatic challenge. The pertinent question is to what extent these perturbations provide a positive stress i.e. improvements in muscle strength, cardiac output, mitochondrial biogenesis etc. and to what extent they are detrimental as a result of overload and or inadequate rest before the next challenge.

For some of our longer-term ICU patients, a daily exercise program is a significant hardship. For example, Denehy's patients refused exercise sessions in 168 of 836 sessions (20%) [135]. Although there are no published reports of patient experience of exercise or rehabilitation in the ICU, the daily actuality of therapists within our centre is that of patients needing significant motivation to engage in exercise programs. Therefore, there is considerable benefit from knowing the minimum required to gain benefit. For example, in the free living population there is increasing evidence that low volume sprint interval training may be as beneficial as traditional endurance training. Clearly, this has a potential application in a group of patients who are only able to tolerate exercise for very short periods of time, and who may already be exercising at near-maximum relative exercise intensity [162, 163]. Despite this knowledge, there are very few exercise parameter recommendations for such patients [143, 164, 165].

Given the multifaceted nature of the impairments responsible for the physical function deficits, an intervention that engages a patient and includes a cardiovascular, musculoskeletal and metabolic challenge is most likely to have an impact. However, the level at which an intervention actually becomes a training load and when it becomes excessive, will be dictated by the patient's duration of exposure to both bed rest and sepsis, along with their incumbent level of physiological fitness before they arrive in ICU.

Study	Location	Age	n	Duration of MV	Illness severity	Control (C)	Intervention (I)	Outcome
(Nava (1998) [130]	Italy RCU	66 (58-76)	80	5-19	P:F 34	FR	PR & progressive mobility program including treadmill	LOS 38 ± 14 days vs. 33.2 ± 11, I vs. C 6MWD significantly improved (p <0.001) in I group only
Zanotti (2003) [133]	Italy RCU (COPD)	66 (60-70)	24	≥30	Not available	Active limb mobilisation	EMS 30 minutes BD for 28 days	Days to 1st BCT I vs. C 10.75 ± 2.41 vs.14.33 ± 2.53 (p <0.001)
Chiang (2006) [134]	Taiwan	76 (63-80)	20	52 (22-80)	Respiratory Failure resolved	Bed Rest	Functional rehabilitation	Significant decrease in FIM in Cs & increased significantly in Is
Schweickert (2009) [119]	USA	55 (36-69)	104	1-2	APACHE II 20 (16-24)	Nothing	OT & PT	Increase no. of ventilator free days at D28. Median walking distance at hospital dc 0 m vs. 30 m

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Study	Location	Age	n	Duration of MV	Illness severity	Control (C)	Intervention (I)	Outcome
Burtin (2009) [128]	Belgium	59 (42-81)	90	4-14	APACHE II 26 (20-42)	FR	Cycle ergometry	PF section of SF36 & 6MWD improved at hospital dc compared to standard PT group
Routsi (2010) [124]	Greece GICU	60 (40-90)	105	>1	APACHE II 18 ± 5	Unclear	EMS	Decreased incidence of CIPNM in EMS group
Brummel (2014) [126]	USA	60	87	3	24 (17.5-31)	UC	PT or PT & CT	No difference
Davis (2013) [125]	USA	76	15	3	APACHE II 23.4 (3.7)	UC	Early Mobility Program	Intervention feasible & safe
Denehy (2013) [135]	Australia GICU	150	60.1(15.8)	5-11	APACHE II 20.7 (7.7)	Mobility exercise 7 days/week	Individualised Exercise prescription	No difference in 6MWD or TUG between C & I

Table 2.1: Prospective randomised controlled trials. Rehabilitation Interventions. RCU = Respiratory Care Unit, C = Control, I = Intervention, PR = Pulmonary Rehabilitation, FR = Functional Rehabilitation, MV = Mechanical Ventilation, EMS = Electrical Muscle Stimulation,GICU = General ICU, BCT = bed chair transfer

Study	Location	Age	n	Duration of MV	Illness severity	Design	Intervention (I)	Outcome
Morris (2008) [120]	USA MICU	54 SD(16)	66	2	23.5 ± 8.8	OBS	Mobilisation	UC patients were first out of bed in 11.3 days vs. 5 days for protocol patients (p <0.001).
Thomsen (2008) [129]	USA RICU	57.9 ± 18.1	104	10.3 ± 7.5	18	OBS	Mobilisation protocol	Predictors of increased mobilisation were transfer to their ICU, lower APACHE II, absence of sedatives & female gender
Bailey (2009) [121]	USA RICU	62.5 ± 15.5	103	≥ 4	17 ± 4.8	OBS	Active mobilisation	2.4% no activity on RICU dc, 4.7% could SOEB, 15.3% could BCT 8.2% ambulated <100 feet & 70% mobilise ≥ 100 feet.
Needham (2010) [127]	USA MICU	50 (43-59)	57	10.5 ± 9.9	26 (21-29)	QIP	Various	Decreased benzodiazepine use. Greater no. of mobilisation episodes. Decrease in ICU length of stay by 2.1 days (95% CI: 0.4-3.8)

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Study	Location	Age	n	Duration of MV	Illness severity	Design	Intervention (I)	Outcome
Clini (2011) [132]	Italy RICU	75 ± 7	77	23 ± 3	11.5 ± 4.4	OBS	Supported & unsupported limb exs with ergometer for 15 sessions	Better functional capacity associated with probability of remaining ventilator-free (p = 0.043) & of hospital survival (p = 0.001).
Martin (2005) [131]	USA MICU	58 ± 7	49	18 ± 7	20	OBS	Functional Rehabilitation	Increases in limb muscle strength, 81% could ambulate by hospital dc

Table 2.2: Non-prospective randomised controlled trials. Rehabilitation Interventions. RCU = Respiratory Care Unit, C = Control, I = Intervention, PR = Pulmonary Rehabilitation, FR = Functional Rehabilitation, MV = Mechanical Ventilation, EMS = Electrical Muscle Stimulation, MICU= Medical ICU, dc = discharge

Chapter 3

Quantifying the exercise load of rehabilitation interventions

In the previous chapter I identified the need for a reliable means of quantifying interventions for the purpose of developing a dose for testing the effectiveness of different rehabilitation strategies. Much work has been done within the field of sports science to optimise training programs of elite and non-elite athletes. There is much that the critical care community could draw upon to optimise rehabilitation strategies to balance the stress of exercise with periods of recovery, thus preventing under- or over-training of individual patients.

3.1 The known physiological response to exercise in ICU patients

Before rehabilitation became the focus of physiotherapy interventions in ICU, two studies looked at the effect of mobilising patients on respiratory parameters. Zafiropulous et al looked at the impact of mobilising 17 post-operative surgical patients who remained ventilated on their first post-operative day [166]. They found a 40% mean increase in minute ventilation ($\dot{V}_E$) in the transition from supine to standing (13% tidal volume (V_T) and 14% respiratory rate (RR)), (*Table 3.1*). There was no further increase when sitting out of bed or marching on the spot.

Activity	$\dot{V}_E$ (L.min^{-1})	V_T (mL)	RR (bpm)
Supine	15.1 ± 3.1	712.7 ± 172.8	21.4± 5
Standing	21.3 ± 3.6	883.4 ± 196.3	24.9 ± 4.5

Table 3.1: Changes in $\dot{V}_E$ with rehabilitation. Zafiropulous (2004).

Similarly, Chang et al [167] assessed the respiratory impact of the tilt-table procedure on 15 patients with chronic critical illness. Patients had received mechanical ventilation for 5-37 days, seven were self-ventilating and all had an F_iO_2 $\leq$0.4. They found a 27% increase in $\dot{V}_E$, (19% increase in RR, 17% increase in V_T). No metabolic parameters were measured. They comment that, as no increase in oxygen consumption ($\dot{V}O_2$) has been reported in healthy individuals when tilt-tabled with the straps attached, they would not have expected an increase in metabolic rate in ICU patients. This is, in part, supported by Collings et al [168] who found non-significant changes in $\dot{V}O_2$ when passively sitting patients out in a chair, while they observed significant increases in $\dot{V}O_2$ when patient's actively performed SOEB (*Table 3.2*). However, the robustness of this study is difficult to establish as insufficient information regarding respiratory exchange ratio (RER)[1] is provided to establish reliability of the results. A rough calculation would suggest that some of the RERs would have been considerably lower than expected.

Activity	Stage	$\dot{V}O_2$ Mean (95% CI) ($mL.min^{-1}$)	$\dot{V}CO_2$ Mean (95% CI) ($mL.min^{-1}$)
PCT	Rest	270(224-315)	166(134-199)
	Sitting	284(241-328)	174(126-222)
SOEB	Rest	262(201-322)	171(131-211)
	Sitting	353(303-402)	206(151-611)

Table 3.2: $\dot{V}O_2$ and $\dot{V}CO_2$ values during passive and active rehabilitation. Collings et al (2015).

A recent Brazilian study [169] has looked at the impact of the tilt-table procedure on the cardiac parameters of 17 non-sedated patients with admission APACHE II scores (mean $\pm$ SD) of 26 $\pm$ 5.37 who were weaning from mechanical ventilation. They report mean arterial pressure (MAP), heart rate (HR) and RASS[2] on Day 1 and 2 and then on the last day of ICU admission. On the first day of tilt-table patients demonstrated a 6% reduction in MAP at 60° tilt, with no increase in HR; on the 2nd day, a 13% drop in MAP and a 4% rise in HR was seen at 90° tilt. These cardiovascular perturbations were not associated with a deterioration in RASS. While these changes were reported as insignificant, they do not represent a normal response to exercise. By ICU discharge MAP was stable with a 4% rise in HR.

[1] RER = $\dot{V}CO_2/\dot{V}O_2$, in steady state RER = RQ, which is the ratio of CO_2 output to O_2 uptake per unit time.

[2] RASS, the Richmond agitation score[170] categorises patients from -5 (unarousable, no response to voice or physical stimulation) to +4 (combative, overtly combative or violent, immediate danger to staff).

Another Brazilian group [142] have just reported on the metabolic, respiratory and cardiac changes seen in 19 sedated patients undergoing 20 minutes of passive cycling starting on day 1 of ICU admission. Patients were aged 55 ± 17 years with SOFA 6 ± 3, P_aO_2/F_iO_2 = 29 ± 7.5 and 13 (68%) required norepinephrine. While they conclude there were no overall cardiovascular or metabolic consequences of passive leg-cycling, their results show considerable individual patient variation in the reported values. For example, while the mean change in cardiac output from rest to exercise was 1%, the range was -16 to +15%; while there was no mean change during recovery the range was -9 to +27%. The mean change in MAP from rest to exercise was 0.8%, but ranged from -16 to +8% and 0.6% during recovery range (-13 to +13%). The $\dot{V}O_2$ at rest was 185.7 $mL.min^{-1}$, with no mean change during exercise but a range of -9 to +21%, and 2% during recovery with a range -25 to +31%. These values suggest that there is considerable individual variation in the cardiovascular response to passive cycling.

Hickman et al [171] looked at the metabolic cost of leg cycling at 0, 3 and 6 watts in patients recovering from critical illness compared to healthy individuals. Only 2/17 of the 6 watt group were mechanically ventilated, none of the 3 watt group and 13/15 of the 0 watt group. Patients who were unable to cycle actively were allocated to the 0 watt group; this sub-group had a higher APACHE II score. They found no statistical difference in $\dot{V}O_2$ between controls and patients during passive cycling or cycling at 6 watts. However, they did find a difference between patients and controls at 3 watts, the increment in $\dot{V}O_2$ was 38.5 ± 14.2% vs. 28.6 ± 6.9%, ($p = 0.04$). They did not give details regarding the accuracy of their ergometer at such low power outputs, nor did they give details of the speed (revolutions per minute) achieved by individual patients.

The little that is known about the exercise response of patients with, or recovering from, critical illness suggests that there is considerable inter-patient variation in the response to very low exercise loads.

3.2 Current methods of exercise prescription in the critically ill

In the absence of an an agreed method of exercise prescription, therapists continue to take a Gestalt approach to terminating rehabilitation interventions. In a postal survey of 111 Physiotherapists working in Australian ICUs, the five most frequently used parameters to decide when to begin, progress and cease exercise were blood pressure, heart rate, oxygen saturation, respiratory rate, and arterial blood gases (ABGs). However, there was no recom-

mended way to utilise these [146].

Two recent papers have made recommendations based on expert consensus for the safe limits of exercise for mechanically ventilated patients. While providing frameworks for rehabilitation none of the parameters suggested have been validated in the mechanically ventilated population nor do they give an indication of either relative or absolute exercise intensity [143, 164].

The Physical Function ICU Test (PFIT) was developed as a sub-maximal test that could be used both as an outcome measure and as a way to prescribe exercise [172, 173]. Originally it had four components, representing the four domains thought to be amenable to exercise training;

- Level of assistance required to sit to stand (0-3 people).
- Steps, duration and cadence of marching on the spot (MOS) at a rate of perceived exertion (RPE) of 3-5 of the modified Borg scale [174].
- Shoulder flexion duration that maintained >90°flexion and >2 seconds between repetitions.
- Muscle strength, (using the 0-5 Oxford scale [175]) for knee extension and shoulder flexion.

The shoulder flexion section has since been removed and PFIT is now scored on sit-to-stand (STS), cadence of marching and muscle strength. The authors advocate its use as a way to set exercise intensity, by utilising 70% of the duration of the MOS time. If unable to MOS then the patient performs STS until unable to continue without assistance. While the authors have demonstrated its responsiveness in a small cohort of the ICU population, it clearly has a floor effect by virtue of the need to stand even before the patient can be assessed. Indeed, in their population it had a 20% floor and ceiling effect.

A real time quantification of how hard a patient is working, or a measurement of their "exercise intensity," would allow clinicians to make a informed judgement as to whether to continue with an intervention or to allow the patient to rest.

3.3 Current methods of exercise prescription in healthy individuals

Outside critical care the three most common ways to prescribe exercise and its intensity are through heart rate derived measures, metabolic equivalents and rate of perceived exertion, all of which are estimates of oxygen consumption ($\dot{V}O_2$).

3.3.1 $\dot{V}O_2$ measurement

Muscular work requires an integrated physiological response of the ventilatory and cardiovascular systems to the increased metabolic demand in order to maintain homeostasis. $\dot{V}O_2$ can be measured via double labelled water, Douglas bag collection, mixing chamber or breath-by-breath-gas exchange-analysis (BBGEA). The latter is the gold standard exercise capacity measurement as it provides a direct measurement of oxygen consumption during exercise (see chapter 4 for a description of the techniques). To standardise the measurement of exercise capacity and the prescription of exercise intensity, either a treadmill or arm/leg ergometers are usually employed to generate a quantifiable stimulus. Such stimuli are usually either constant load or incremental tests, from which a variety of different surrogates of exercise capacity and intensity can be obtained. Incremental tests have an increasing load throughout. For example, unloaded cycling for 1 minute, then 5 watts for 1 minute and increasing by 5 watts.min^{-1} until the end of the test. An estimate is made of the individual's peak $\dot{V}O_2$ and the protocol is adjusted to keep the test duration between 8-10 minutes. Constant load protocols maintain the same work level throughout the test and, depending on the method of interpretation may involve a series of increasing constant loads to establish peak $\dot{V}O_2$ or maximum work in watts.

3.3.1.1 Peak $\dot{V}O_2$

The peak value of $\dot{V}O_2$ reached during an incremental or ramp test provides information regarding an individual's exercise capacity that is comparable both between and within patients. An increase in peak $\dot{V}O_2$ indicates an improvement in exercise capacity, although this may also indicate an increase in patient motivation. $\dot{V}O_2$ peak can be used to derive parameters to prescribe exercise, i.e. a target heart rate or work rate can be determined at which the subject is known to be working at proportion of their $\dot{V}O_2$ peak.

3.3.1.2 $\dot{V}O_2$max

$\dot{V}O_2$max is more difficult to obtain than peak $\dot{V}O_2$ during an incremental test due to uncertainty regarding the reason for cessation of exercise. It can be most reliably be obtained from discontinuous constant workload tests where failure to increase $\dot{V}O_2$ despite an increase in

work rate indicates the actual $\dot{V}O_2$max. $\dot{V}O_2$max is unlikely to be reliably or safely achieved in ICU patients.

3.3.1.3 Anaerobic threshold

Anaerobic threshold (AT) is the $\dot{V}O_2$ at which an individual moves from aerobic to anaerobic metabolism during exercise. It is usually identified from a ramp or incremental test, but it can also be estimated from a series of constant-load tests. In healthy individuals, if steady-state (identified by a plateau in $\dot{V}O_2$) has not been achieved within three minutes of exercise, it is assumed that they are working above their AT. If AT can be identified it can be used to prescribe exercise intensity i.e. if the HR or work-rate at which the patient reaches AT can be identified, this can be used to steer a training stimulus. Additionally, it can be used to monitor exercise capacity. An increase in AT would indicate an improvement in exercise capacity.

3.3.1.4 Oxygen uptake efficiency slope

Oxygen uptake efficiency may be a useful sub-maximal indication of cardiorespiratory reserve. The oxygen uptake efficiency slope (OUES) is defined by the logarithmic regression line describing the relationship between $\dot{V}O_2$ and minute ventilation ($\dot{V}_E$) representing the $\Delta\dot{V}O_2$, in response to a given change in $\dot{V}_E$. It therefore represents the absolute increase in $\dot{V}O_2$ associated with a 10-fold rise in ventilation.

$$\dot{V}O_2 = a * log\dot{V}_E + b \begin{cases} \text{where the units of } VO_2 \text{ are } mL.kg.^{-1}min^{-1} \\ \text{and } \dot{V}_E \textit{ is } L.kg.^{-1}min^{-1} \end{cases} \tag{3.1}$$

Thus, OUES is a variable that indicates how effectively oxygen is extracted by the lungs and taken into the body. Importantly, OUES is an index of physical fitness that is independent of the motivation of the patient to perform maximal exercise [176]. A change in the slope of the OUES may indicate a change in the patient's physical fitness. If a clear relationship between $\dot{V}O_2$ and $\dot{V}_E$ can be established it may also be possible to use $\dot{V}_E$ as a surrogate of $\dot{V}O_2$.

3.3.1.5 Oxygen uptake kinetics

Uptake of oxygen during exercise is classically divided into three stages. During exercise below the AT, phase I of exercise is characterised by an immediate increase in $\dot{V}O_2$. This is thought to be in response to the abrupt increase in pulmonary blood flow and an increase in HR and stroke volume (SV). Phase II lasts from about 15 seconds to 3 minutes and phase III represents a steady state where $\dot{V}O_2$ increases linearly with work rate during incremental tests or plateaus during constant load tests. The mean $\dot{V}O_2$ response time (MRT); the time constant of the exponential rise in $\dot{V}O_2$ (63% of the asymptotic response), can be used to

quantify the $\dot{V}O_2$ kinetics of the response to exercise. The MRT decreases as physical fitness increases, but it would only be useful for monitoring change in exercise capacity rather than accurately setting an exercise intensity. However it would provide an indicator of the level of a patient's physical deconditioning.

3.3.1.6 Excess post-exercise oxygen consumption

During the recovery period after exercise $\dot{V}O_2$ remains elevated and is termed excess post-exercise oxygen consumption (EPOC). It reflects the level of anaerobic metabolism in the previous exercise bout and the circulatory, hormonal and thermal adjustments that are inherently necessary in the restoration of homeostasis. EPOC consists of fast and slow components. The metabolic consequences of exercise are dependent on both the intensity and duration of the exercise which in turn, are related to the duration and magnitude of EPOC. The relationship between the magnitude of EPOC and intensity is curvilinear, with a linear relationship between duration of exercise and magnitude of EPOC at high intensities. Therefore, a single constant-load test repeated at set intervals would provide the data to track an individual's cardiorespiratory fitness over time. Additionally, once an acceptable recovery period was defined, sequential tests of increasing workload would identify a level at which to set the intensity of an exercise session.

3.3.2 Lactate

An increase in blood lactate is a key feature of high intensity exercise [177]. The magnitude of the increase is dependent on the level of fitness of the individual [178] plus factors that affect the uptake, transport or extraction of oxygen e.g. mitochondrial, lung or cardiac disease and the rate of metabolism of lactate [179–181]. It is also important to consider potential acclimatisation of patients to their hypoxic state and the impact this may have on accumulation of lactate [182]. Lactate starts to accumulate in muscle and blood only when a critical capillary oxygen partial pressure is reached. The net increase in anaerobic glycolysis required for the re-oxidation of nicotinamide adenine dinucleotide (NADH) to NAD^+ lowers the mitochondrial cytosolic redox state, resulting in an accumulation of lactate in muscle and blood. While exercise remains aerobic the rate of removal of lactate by other tissues matches its rate of production [183]. For healthy untrained persons, lactate accumulation and its subsequent exponential rise occurs at about 55% of the individual's capacity for aerobic metabolism. Adaptation within muscle from aerobic training enables high rates of lactate turnover. Thus, lactate only begins to accumulate at higher intensity levels than in the previously untrained state. Serial measurements of lactate can be obtained during a ramp protocol to establish the onset of blood lactate accumulation (OBLA), defined as a systematic increase of blood lactate

equal to 4.0 mM [184]. OBLA allows an estimation of the HR below which the individual can be assumed to be exercising aerobically which, in a normal individual, would indicate a $\dot{V}O_2$ of 60-80% of their maximum. Hence, it should be possible to prescribe absolute work intensities for individual patients based on the work intensity at which OBLA occurs. Exercise capacity could be monitored by repeating the same test, and monitoring the change in work rate before OBLA.

As BBGEA and lactate measurement are not readily available outside of the laboratory, the three most common ways to prescribe exercise and its intensity are through HR derived measures, metabolic equivalents and rate of perceived exertion, which have all been developed as proxies for oxygen consumption.

3.3.3 Heart rate derived measures

3.3.3.1 Heart rate maximum

There is a clear linear relationship between HR and $\dot{V}O_2$ in the normal population [185], with an error in estimating $\%\dot{V}O_2max$ from $\%HR_{max}$ of ± 8% [186]. However, this relationship becomes uncoupled with comorbidities such as heart disease where the HR increase is relatively steep for the increase in $\dot{V}O_2$ due to the relatively low stroke volume in affected patients. In patients with coronary artery disease the $\Delta\dot{V}O_2$ increase slows as the patient becomes ischaemic [187]. In this instance the ΔHR relative to $\dot{V}O_2$ will also become steeper. Additionally, patients with airflow obstruction have a moderately elevated HR for a given $\dot{V}O_2$ due to restrictions in venous filling [188].

Obtaining an accurate value of HR_{max} from an exercise stimulus is not practical or safe in the ICU setting. Although it is possible to estimate HR_{max} from various variable-derived equations, consideration must be given to the accuracy of using such final indices. Additionally the prescription of Digoxin and beta-adrenoceptor blockade precludes use of HR in isolation. For example, the SD of the estimated HR_{max} calculated by 220-Age is 11 beats.min^{-1} [189]. Recently, the validity of the "percentage of maximum" concept for calculating training intensity has been questioned [190]. While this threshold may be appropriate for young individuals of average fitness, subsequent investigators have suggested that the threshold for men in their sixties and seventies should be 40% of heart rate reserve [191].

Karvonen's landmark study in the 1950s identified a minimal level of exercise intensity, above which a beneficial training effect was demonstrable [192]. This set a training threshold at a HR equal to 60% of the difference between resting and maximum, or heart rate re-

serve (HR_{res}). The accuracy of both $\%HR_{max}$ and $\%HR_{res}$ assumes a functional relationship between cardiorespiratory and metabolic markers, and may not be applicable under certain circumstances e.g. beta-adrenoceptor blockade [193]. Unfortunately, there is no evidence on which to model uncoupling of HR from $\dot{V}O_2$ in patients recovering from critical illness. Given the common incidence of COPD, heart failure and ischaemic heart disease in the failure-to-wean from mechanical ventilation population and the length of time taken for cardiac ejection fraction to return to normal, these factors most probably exclude heart rate changes as a reliable indicator of exercise capacity or intensity. Therefore, unless a nomogram can be created for patients in critical care, the use of HR to prescribe exercise from estimated maximums has little value.

3.3.3.2 Heart rate recovery

Heart rate recovery (HR_{rec}) typically follows a decreasing mono-exponential pattern [194] quantified by the absolute difference between the HR at exercise completion and after 60 or 120 seconds of recovery (T_{60}, T_{120}), or the time constant (HRRπ) of the HR decay obtained by fitting the post-exercise HR_{rec} into a first-order exponential decay curve. The rate of HR_{rec} is the consequence of parasympathetic reactivation and sympathetic withdrawal following exercise [195]. Large cohort studies have shown that HR_{rec} is independent of age, gender, and maximum heart rate, and is positively modulated by exercise training in patients with heart disease. Both endurance and strength-trained athletes have a faster HR_{rec} following exercise at similar absolute intensities than untrained subjects [196, 197]. Conversely, slowing of HR_{rec} is associated with acute increases in training load [198] and worsening performance [199]. Data suggest that the kinetics of HR_{rec} differ between maximal and sub-maximal exercise. The initial rapid decline in HR as described by short-term indexes such as T_{30} and T_{60} are considered markers of increased cardiac parasympathetic outflow, which occurs early post-exercise at all intensities [200]. The second, slower HR decay, as depicted by HRRπ, is believed to be workload-dependent [194] and related to the clearance of stress-system metabolites e.g. H^+ and lactate. Following higher levels of exercise, this second decay phase is modulated by sympathetic drive, which continues well into the recovery period, contributing to maintenance of high HR despite parasympathetic activation. The modulation of this second decay phase by high intensity exercise means that HRRπ does not provide an adequate model of HR_{rec} following maximal exercise [201].

The within-subject day-to-day variation in HR for a given exercise intensity decreases with increasing exercise intensity [202]. Imai et al [203] investigated the workload dependence of T_{30} and T_{120} on three levels of exercise intensity (50% of anaerobic threshold, anaerobic threshold

and at maximal exercise). $\dot{V}O_2$, systolic BP and heart rate at the end of exercise were all increased with increasing workload. This trend was also noted at T_{120}, indicating that this index is largely dependent on the exercise workload. In contrast, T_{30} was nearly independent of exercise intensity, though the value of T_{30} at maximal exercise was significantly greater than that at anaerobic threshold. Gore et al [204] found that T_{30} was also intensity and not duration dependent.

The use of HR_{rec} as a tool to evaluate both exercise capacity and session load requires the development of a population-specific, standardised, sub-maximal test that could be performed on a weekly basis. Such a test would track the impact of exercise strategies on HR_{rec} over time, allowing tailoring of the intensity of exercise for individual patients, and also allow tracking of changes in exercise capacity. Thus, increased HR_{rec} for the same given absolute work intensity exercise would indicate improvement in exercise capacity, allowing comparison both between and within patients.

3.3.3.3 Heart rate variability

The autonomic nervous system is central to an individual's ability to respond to the dynamic challenge of exercise. Heart rate variability (HRV) is a relatively new concept in monitoring both exercise session load and exercise capacity. HRV increases following exercise training, but decreases with over-training. It is measured by the variation in the R-R interval of the ECG. The R-R interval of consecutive beats is calculated and plotted on a tachogram. Signals are then transformed by Fast Fourier Transformation (FFT) waveform analysis into frequency domains.

HRV modulation is considered to be exercise intensity rather than duration dependent [205, 206]. Tulppo et al [207] demonstrated that HRV decreased during exercise almost to the extent that it disappears during high intensity exercise, i.e. the greater the relative exercise intensity, the less variability is seen in the R-R interval. Seiler et al [208] found that doubling exercise duration from 60 to 120 minutes while maintaining exercise intensity in both trained and highly trained individuals had little impact on HRV recovery. Kaikkonen et al [209] also found that doubling the running distance from 3,500 to 7,000 m had no impact on the extent of HRV nor its rate of recovery. However, increasing the training intensity caused slower HRV recovery and lower High Frequency Power (HFP) and Total Power (TP) during the first five minutes of recovery. Conversely, Kaikkonen et al [210] found that a fourfold increase in running distance at 60% $\dot{V}O_2$ max, and an increase in exercise intensity from 60% to 85% decreased HFP, LFP and TP during the first two minutes of recovery. They also found that

decreased post-exercise HRV was closely related to an increase in blood lactate and the RPE.

Recovery of HRV is faster in trained than untrained individuals [208, 209]. In order to use HRV to monitor training load, either HRV could be monitored at rest, over time, or following a set stimulus such as unloaded cycling. Alternatively, HRV could be recorded before, during and after a rehabilitation intervention. Depending on the rate of HRV recovery following the session, the training load (duration or intensity) could be adjusted.

3.3.4 Rate of perceived exertion

There is an extensive literature describing the relationship between RPE and physiological variables during exercise. Although RPE was developed to describe the intensity of exercise, its subjective nature also takes the duration of exercise into account. The most frequently used RPE scale is Borg's 6-20 category scale [211]. Although recommended for use by the Delphi consensus group published by Hanekom et al [164], the use of the Borg scale has not been validated in the ICU population.

3.3.5 Metabolic equivalents

One metabolic equivalent (MET) is defined as the amount of oxygen consumed while sitting at rest and equates to 3.5 $mL.kg.^{-1}min^{-1}$ of O_2. The MET concept expresses the energy cost of physical activities as a multiple of the resting metabolic rate. Therefore, the relative energy cost of an activity can be determined by dividing the oxygen cost of the activity in $mL.kg.^{-1}min^{-1}$ by 3.5. Thus, 1 MET (sitting at rest) equates to about 245 $mL.min^{-1}$ for a 70 kg person. Exercise performed at 2 METs requires twice the energy required at rest. Compendiums of activity with their associated METs are available to estimate a persons' maximum functional oxygen consumption by the most strenuous activity they can complete, giving an indication of their peak $\dot{V}O_2$ [212]. However, given that similar workloads in patients recovering from critical illness have been shown to require a higher MET than in healthy individuals [171], metabolic estimations in a healthy population may not be accurate in patients recovering from critical illness. Additionally, the majority of activities reported in the compendiums take place while individuals are already standing.

3.4 Potential measures of exercise capacity and intensity in patients recovering from critical illness in ICU

Surrogate measures of exercise intensity and capacity are dependent on the development of a reproducible and quantifiable exercise stimulus.

3.4.1 The modality of exercise used to generate the exercise stimulus.

Treadmill, arm and leg ergometry are the modalities generally used during exercise testing. The use of treadmills is clearly not feasible in a patient cohort unable to stand. Prior clinical experience on the ICU at UCH indicated that greater numbers of patients were able to use an arm ergometer than a leg ergometer. However, there are significant differences between the physiological response to arm and leg ergometry. At a given sub-maximal workload, arm exercise is performed at a greater physiological cost than leg exercise, reflected in the greater HR and $\dot{V}O_2$ response in arm vs. leg exercise at identical workloads. It is postulated that this discrepancy is due to reduced mechanical efficiency during arm exercise vs. leg exercise [213, 214]. Anaerobic threshold and peak $\dot{V}O_2$ achieved during arm ergometry tests are reported to be 64%-80% of that achieved during leg ergometry [215, 216]. This is likely to be due to the involvement of smaller muscle groups and the static effort required with arm work, which increases $\dot{V}O_2$ but does not affect the external work output.

Despite these differences, I felt that arm ergometry was sufficiently accepted as a reproducible exercise stimulus in the wider population and that more patients would be recruited using arm than leg ergometry.

3.4.2 Potential exercise tests

There are four possibilities.

i) An incremental ergometry test specifically for mechanically ventilated ICU patients, thus giving the potential to measure $\dot{V}O_2$ peak, OUES and AT. If sufficient patients who are representative of the wider ICU rehabilitation population were able to complete an incremental test, then it may be possible to derive a population-specific equation for HR vs. $\dot{V}O_2$. This would circumvent the need for an initial exercise test to prescribe exercise intensity.

ii) A sub-maximal incremental ergometry test specifically for mechanically ventilated ICU patients. If factors causing patients to stop exercise were unclear it may be possible to use a sub-maximal incremental ergometry test to measure OUES.

iii) A series of constant load tests would allow measurement of oxygen uptake kinetics, EPOC and HRV in addition to $\dot{V}O_2$ peak, OUES and AT.

iv) A single constant load ergometry test would allow measurement of oxygen uptake kinetics, EPOC and HRV.

v) If a clear relationship between $\dot{V}O_2$ and $\dot{V}_E$ can be established, it may also be possible to use $\dot{V}_E$ as a surrogate of $\dot{V}O_2$, with either a constant load or series of constant load tests.

There is a wealth of knowledge and experience within sports and exercise science that the critical care community can draw upon to build a scientific basis for the prescription of exercise interventions in patients recovering from critical illness. Such knowledge will allow us to move away from the "one-size-fits-all" approach we currently employ and to tailor exercise programs to individual patients. We may then begin to understand who has the capacity to respond to a physical rehabilitation intervention and who does not.

3.5 Measuring oxygen consumption in mechanically ventilated patients

There are several ways to measure oxygen consumption in mechanically ventilated patients. The following are the most commonly used and published methods:

3.5.1 Inverse Fick principle

The inverse or reverse Fick technique is perhaps the most commonly used method to measure oxygen consumption in mechanically ventilated patients in ICU. Originally, the Fick principle [217] was used to calculate cardiac output from $\dot{V}O_2$ and the arterio-venous oxygen difference, where $\dot{V}O_2$ was an assumed value based on the patient's gender and body weight *(Equation 3.2)*. However, the introduction of the pulmonary artery catheter as a bedside tool for measuring cardiac output through thermodilution allowed the calculation of oxygen consumption from cardiac output and the arterio-venous oxygen difference (*Equation 3.3*).

$$\text{Cardiac output} = \frac{\dot{V}O_2}{\text{arterio-venous } O_2 \text{ difference}} \left\{ \text{ Fick equation} \right. \tag{3.2}$$

$$\dot{V}O_2 = \text{Cardiac output*arterio-venous } O_2 \text{ difference} \left\{ \text{ Inverse Fick equation.} \right. \tag{3.3}$$

The development of oesophageal Doppler (and other techniques) now negates the need for a pulmonary artery catheter to measure cardiac output, but it is still necessary for accurate measurement of mixed venous oxygenation [218]. Very few patients recovering from critical illness will have a pulmonary artery catheter in situ, thus it is unsuitable for monitoring during exercise.

3.5.2 Double-labelled water

Double-labelled water uses water labelled with deuterium (^{2}H) and oxygen-18 (^{18}O), or deuterium oxide ($D_2{}^{18}O$). Metabolic rate can be estimated by measuring the elimination rates of deuterium and ^{18}O by the regular sampling of heavy isotope concentrations in saliva, urine, or blood. When O_2 in water is labelled with ^{18}O, the CO_2 produced by respiration contains labelled O_2. Additionally, the ^{18}O equilibrates in bicarbonate and the dissolved carbon dioxide pool (through the action of the enzyme carbonic anhydrase). ^{18}O is lost from the body in CO_2 and through urine and insensible losses. However, deuterium is lost only through urine and insensible losses. Thus the loss of deuterium can be used to mathematically compensate for the loss of ^{18}O by the water-loss route. The net loss of ^{18}O in CO_2, provides an estimate of the CO_2 production the between the samples. However, knowledge of the RQ is required and measurements can only be made over long periods of time.

3.5.3 Open-circuit indirect calorimetry

Open-circuit indirect calorimetry is the measurement or derivation of oxygen consumption and carbon dioxide production from values obtained from the analysis of inspired and expired gas *(Equation 3.4 and 3.5)*.

$$\dot{V}O_2 = (\dot{V}_I \cdot F_iO_2) - (\dot{V}_E \cdot F_eO_2) \left\{ \text{Oxygen consumption} \right. \tag{3.4}$$

$$\dot{V}CO_2 = (\dot{V}_E \cdot F_eCO_2) - (\dot{V}_E \cdot F_iCO_2) \left\{ \text{Carbon dioxide production} \right. \tag{3.5}$$

One of the biggest challenges when measuring pulmonary gas exchange is the precision required of the values for inspired and expired $\dot{V}_E$. Both volumes must be measured, with an inherent error associated with subtracting two potentially inaccurate values. Alternatively, inspired or expired volume must be measured and the Haldane equation *(Equation 3.6)* used to calculate the remaining value *(Equation 3.7)*. This equation makes the assumption that nitrogen is neither produced nor retained by the body and that no other gases are present

other than oxygen, carbon dioxide and nitrogen.

$$\dot{V}_I \cdot F_iN_2 = \dot{V}_E \cdot F_eN_2 \left\{ \text{Haldane equation.} \right. \tag{3.6}$$

$$\dot{V}_I = \dot{V}_E \cdot \frac{F_eN_2}{F_iN_2} \left\{ \begin{array}{l} \text{Calculation of inspired volume} \\ \text{using the Haldane equation.} \end{array} \right. \tag{3.7}$$

$$\dot{V}_I = \dot{V}_E \cdot \frac{(1 - F_eCO_2 - F_eO_2)}{1 - F_iO_2} \left\{ \text{Substitution of known values.} \right. \tag{3.8}$$

$$RQ = \frac{(1 - F_iO_2)}{\frac{(F_iO_2 - F_eO_2)}{(F_eCO_2)} - (F_iO_2)} \left\{ \begin{array}{l} \text{Transformation of} \\ \text{the Haldane equation} \end{array} \right. \tag{3.9}$$

$$\dot{V}O_2 = \frac{\dot{V}CO_2}{RQ} \left\{ \text{Calculation of } \dot{\text{V}}\text{O}_2 \right. \tag{3.10}$$

Additionally, gas volumes vary with temperature, ambient pressure and humidity. These factors must be accounted for to ensure accurate gas exchange measurements. Most systems use algorithms to adjust for gas volumes. Additionally, the device must be correctly calibrated and correct conditions entered into the analysis software to ensure accurate results. However, there are other potential sources of error that require consideration when evaluating such devices:

i) How the device handles flow-by or bias-flow, which is an integral system in most modern ventilators, can lead to a significant bias in all obtained values. Bias-flow or flow-by is the delivery of a continuous flow of gas, usually in the order of 2 L.min^{-1} of the pre-set concentration of oxygen, through the patient's ventilation circuit. Bias flow is considered to reduce the sensation of air hunger experienced by the patient during the breath trigger phase of the breathing cycle. Mishandling of this extra volume of oxygen added to the expired volume can significantly impact upon the values obtained.

ii) Although the precision of the gas analysers of most modern systems is no longer considered a major confounding factor, the response time of the gas analysers is. Breath-by-breath systems must cope with the rapid and irregular breathing patterns of the tachypneoic ventilated patient. This necessitates a response time of 0.15-0.2 seconds to accommodate respiratory rates of 40-50 bpm [219].

iii) The high pressures generated by mechanical ventilation in the inspiratory limb of the ventilator circuit can significantly alter gas partial pressures. Therefore, a single gas analyser must be able to measure gas presented under different conditions and apply a correction factor dependent on the pressure measured in the sampling tube.

iv) The difference in inspired and expired concentrations of oxygen becomes proportionally smaller as the concentration of the inspired gas increases. Thus, increasing inspired

oxygen concentration may introduce further inaccuracy if the system is reliant on the Haldane equation. Additionally, instability of the fraction of inspired oxygen (F_iO_2) during inspiration is difficult to control in most modern ventilators, but does need to be monitored and accounted for during analysis of collected values. As most systems rely primarily on collection of expired gas volume, leaks from the ventilator circuit can introduce significant error.

There are three methods of measuring pulmonary gas exchange in mechanically ventilated patients: Douglas bag collections, the mixing chamber and breath-by-breath-gas exchange analysis.

3.5.4 Douglas Bag Collection

This first method of calculating oxygen consumption was described in 1911 by Gordon Douglas, an Oxford physiologist. All gas expired by a subject is collected into gas collection bags (now made of PVC). Samples of this expired gas are extracted from the bag and the CO_2 and O_2 content analysed [220]. The volume of gas is then measured and the volume of O_2 extracted and CO_2 produced calculated *(Equations 3.4 and 3.5)*. This is feasible with mechanically ventilated patients but does present several challenges especially with respect to the handling of conditions presented to the gas, and the partial pressure of inspired oxygen [221]. While cumbersome, and time consuming, Douglas bag collections (DBC) do provide a means of validating other methods of measuring $\dot{V}O_2$.

3.5.5 Deltatrac II

An alternative method is to use an automated indirect calorimetry device such as the Deltatrac II (Datex−Omeda, Finland). This measures the concentration of inspired and expired oxygen and carbon dioxide, and measures or calculates the inspired and expired volumes of gas.
The Deltatrac II is possibly the most widely used indirect calorimeter in the critical care setting. It circumvents potential error introduced by measuring or calculating expired minute ventilation ($\dot{V}_E$) and calculating inspired minute ventilation ($\dot{V}_I$) by using a transformation of the Haldane equation (*Equation 3.9*).

Deltatrac $\dot{V}CO_2$ calculation.

$$\dot{V}CO_2 = F_dCO_2 * 40 \begin{cases} \text{Where } F_dCO_2 \text{ is the fraction of} \\ \text{expired and diluted carbon dioxide} \\ \text{and 40 is the flow constant.} \end{cases} \quad (3.11)$$

Therefore:

$$\dot{V}O_2 = \frac{\dot{V}CO_2}{RQ} \quad (3.12)$$

The device is an open-circuit calorimeter with two chambers. The first collects and mixes the gas expired by the patient. Gas is sampled from this chamber and the fraction of expired O_2 and CO_2 analysed. The expired gas is then drawn through an air dilution chamber at a constant flow rate. In most machines this is roughly 40 L.min^{-1} but there is variation between and within machines over time, necessitating regular calibration. The gas is sampled from the air dilution chamber and the fraction of CO_2 analysed allowing calculation of the original volume of CO_2 expired by the patient.

The Deltatrac was first described by Meriläinen [222] in 1987. Takala et al [223] published the first clinical validation study comparing $\dot{V}O_2$ values obtained from indirect Fick measurements and the Deltatrac II in 20 patients following cardiac surgery who were ventilated in controlled mandatory ventilation (CMV) mode, and 10 tests in 5 patients ventilated with synchronised intermittent mandatory ventilation (SIMV). The mean ± SD $\dot{V}O_2$ obtained by indirect calorimetry was consistently higher than with inverse Fick (294 ± 59 vs. 247 ± 58), a mean difference of 49 ± 25 mL or 16 ± 9% ($p<0.01$). This error was magnified to 25 ± 8% when patients were ventilated in SIMV. Increasing F_iO_2 from 0.4 to 0.6 during stable ventilation did not make a significant difference to either $\dot{V}CO_2$ or $\dot{V}O_2$ values. The authors concluded that the error was acceptable for clinical practice given that a previous study using DBC [224] gave a 15% greater value for $\dot{V}CO_2$ obtained from indirect calorimetry. Tissot et al [221] compared the Deltatrac II with both DBC and mass spectroscopy (MS) in 35 mechanically ventilated patients. They found a much smaller -3.5 ± 2.5 mL (DBC) and -5.8 ± 1.6 mL (MS) $\dot{V}CO_2$ error.

For the last two decades the Deltatrac II has remained the "gold standard" against which the majority of new devices have been compared. However, there has been little consistency demonstrated in the margins of error between the Deltatrac II and other devices [225–227].

3.5.5.1 Breath-by breath-gas exchange analysis

Until recently, BBGEA technology has struggled to manage the flow-by system of modern ventilators. A number of new gas exchange analysis devices have become commercially available but they have yet to be validated in the ICU population. The MedGraphics Ultima (MGU) is one such device that provides breath-by-breath analysis of gas exchange. It has been validated and is widely used for exercise testing in spontaneously breathing patients, but has yet to be validated in mechanically ventilated patients. It has however been shown to be unaffected by "bias flow" in a lung simulator model [228]. The system measures both inspiratory and expiratory flow, and thus does not require the Haldane equation. It achieves this through a bi-directional, patented flow-sensor. The oxygen analyser is a fuel cell with a response time <80 ms while the carbon dioxide analyser is a non-dispersive infra-red sensor with a response time <150 ms. The system samples gas continuously and phase-aligns the oxygen and carbon dioxide signals with the flow signal to calculate inspired and expired values for CO_2 and O_2 *(Figure 3.1)*. There are three potential sources of error for the measurements

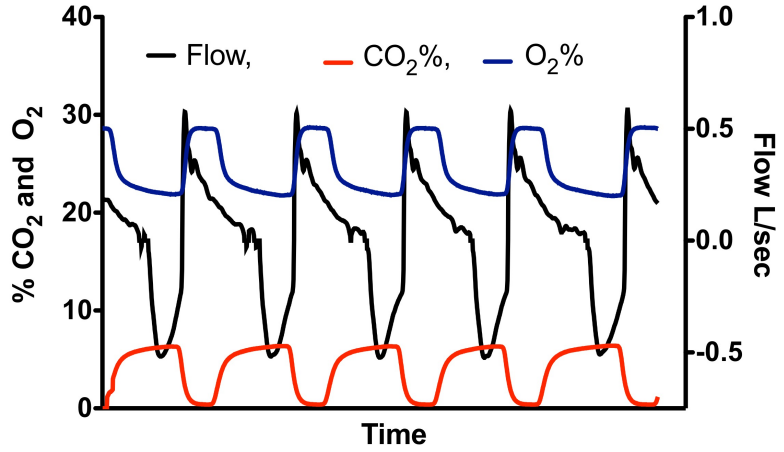


Figure 3.1: Phase alignment of MGU flow, CO_2 and O_2 signals.

made with the MedGraphics Ultima (MGU). 1. Volume measurements. 2. Oxygen and carbon dioxide gas concentration analysis. 3. Handling of humidity and temperature of *in vivo* measurements.

3.6 Summary

The ideal way to measure exercise capacity and intensity in mechanically ventilated patients would appear to be through measurement of $\dot{V}O_2$. The only feasible techniques to do this are DBC, or indirect calorimetry. The DTII has been widely used in mechanically ventilated patients at rest, but not during exercise and only gives measurements on a minute-by-minute basis. DBC are cumbersome and time-consuming and only measure over 5 minute periods. Before BBGEA can be used in this population, it requires validation.

Chapter 4

Validation of the MedGraphics Ultima

There is no precedent for the validation of BBGEA systems during exercise in mechanically ventilated patients. While studies have measured $\dot{V}O_2$ and $\dot{V}CO_2$ during rehabilitation interventions, no details regarding the precision, bias or reproducibility of the measurements have been provided [142, 168]. The gold standard for automated gas-analysis system validation during exercise is the Douglas bag technique to analyse the gas generated from a reproducible exercise stimulus. This is unfeasible, given the development of a reproducible exercise stimulus was one of the objectives of my research. The MGU is validated for use in a dynamic environment but not for use during mechanical ventilation. The gold standard for measuring gas exchange in mechanically ventilated patients is the Deltatrac II which requires that the patient be in steady state during the measurements. Therefore, until a reproducible stimulus could be established, the only realistic validation technique was to compare Douglas bag collections, Deltatrac II measurements and the MGU, with the patient in steady state. *Table 4.1* lists the main issues using a system designed primarily for exercising athletes in mechanically ventilated patients.

4.1 MedGraphics Ultima familiarisation

The paucity of data available to support the accuracy of the MGU device required a series of tests be performed to investigate the precision of the device, before beginning a direct comparison with Douglas bag collections and the Deltatrac II, to then establish accuracy.

Precision and response time of the gas analysers
High pressures within the inspiratory limb of the ventilator circuit
Leaks from the ventilator circuit
High inspired oxygen concentrations
Need for meticulous calibration and for correct ambient conditions entered into the analysis software
Handling of bias flow (flow-by) from the ventilator
Instability of the fraction of inspired oxygen (F_iO_2) during inspiration
Dead space created by the ventilator tubing and heat moisture exchange systems
High signal-to-noise ratio due to relatively low levels of $\dot{V}O_2$

Table 4.1: Challenges associated with indirect calorimetry monitoring.

4.1.1 Gas exchange system validator

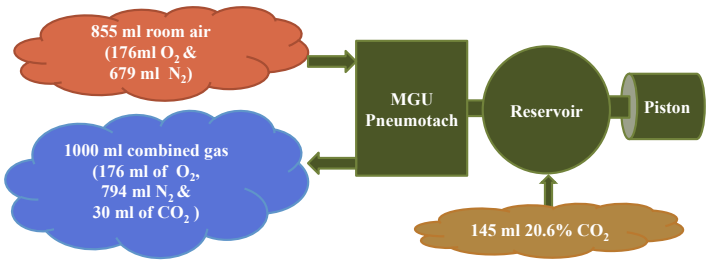
Gas exchange system validators (GESV) simulate respiratory gas exchange for verification of cardiopulmonary gas exchange measurement systems [229]. These have been developed for quality control of gas exchange measurements using automated systems. Gas exchange simulators do not simulate the normal variation in breathing pattern waveforms nor do they simulate moist, room temperature exhalate. Thus, the effectiveness of drying exhaled air before analysis, or application of temperature and humidity corrections, are not tested. Therefore, these calibrators are perhaps most useful for the detection of variations in performance of the system (precision) rather than accuracy.

Theoretically, if all the inspired O_2 were extracted from room air during a metabolic process, assuming a respiratory quotient (RQ)[1] of 1, approximately 20.6% CO_2 would be produced. Hence, if a standard metabolic calibration medium of 20.6% CO_2 and 79.4% N_2 is used, the potential error when calculating inspiratory from expiratory volumes is negated. One litre of gas simulates metabolism of 210 mL.min^{-1} for both $\dot{V}O_2$ and $\dot{V}CO_2$. The MedGraphics GESV draws in room air (21.6% O_2 and 79.4% N_2) through the flow sensor (*Figure 4.1a*). Downstream of the flow sensor a precision gas (21.6% CO_2:79.4% N_2) is bled into the room air within the reservoir. At the end of the inspiratory cycle the gas is then pushed back through the flow sensor. The resulting expired gas mixture has a higher fraction of CO_2 and a lower

[1] RQ=$\dot{V}CO_2/\dot{V}O_2$

fraction of O_2 than the inspired room air, mimicking the expected concentrations of expired gas (*Figure 4.1b*).

(a) MedGraphics gas exchange system validator.



(b) Schematic.

Figure 4.1: MedGraphics gas exchange system validator.

Thus if an 855 mL inspiratory "breath" comprises:

- 176 mL O_2 = 20.6%*855 mL and
- 679 mL N_2 = 79.4%*855 mL.

The 1000 mL expiratory "breath", will have:

- 30 mL CO_2 = 20.6%*145 mL and
- 115 mL N_2 = 79.4%*145 mL added.

Hence the expired gas will be:

- 17.6% O_2, 3% CO_2 and 79.4% N_2.

Assuming 10 breaths.min^{-1}:

- 2060 mL.min^{-1} O_2 will be inspired and 1760 mL.min^{-1} O_2 expired.

Resulting in:

- 300 mL.min^{-1} of $\dot{V}O_2$ and $\dot{V}CO_2$.

The system has two variables, each with three possible values each; V_T (0.5 L, 1.0 L and 1.5 L) and respiratory rate (10 bpm, 20 bpm and 40 bpm). This provides a range of flows and volumes seen in patients at rest and during exercise *(Table 4.2)*.

4.1.1.1 Objective

To evaluate the precision of values obtained for $\dot{V}O_2$ and $\dot{V}CO_2$ with different flow rates generated by a gas exchange system validator.

Breaths per	Duty cycle	Expiratory time	Tidal Volume		
minute	(Sec)	(Sec)	0.5(L)	1.0(L)	1.5(L)
10	6	3	10	20	30
20	3	1.5	20	40	60
40	1.5	0.75	40	80	120

Table 4.2: Gas flow in litres per minute generated by the lung simulator.

4.1.1.2 Method

The GESV was connected to the MGU and 13 trials (*Table 4.3*) were used to simulate six different flows and volumes that characterise the inspiratory flows and volumes of mechanically ventilated patients. Each trial was conducted for five minutes and the average of the last three measurements for both $\dot{V}O_2$ and $\dot{V}CO_2$ were used for comparison with the calculated expected values.

Trial	BPM	V_T	Flow
	(L)		($L.min^{-1}$)
1	10	1	20
2	20	1.5	60
3	10	1	20
4	20	1.5	60
5	40	1.5	120
6	20	0.5	20
7	10	0.5	40
8	40	0.5	40
9	40	0.5	40
10	40	0.5	40
11	40	0.5	40
12	40	1	80
13	40	1	80

Table 4.3: GESV trials, V_T, breaths per minute and flow.

4.1.1.3 Analysis

4.1.1.4 Analysis

The mean values from the 13 tests were plotted as a percentage of the expected values for each individual test. *(Appendix A.1)*. No analysis was carried out to establish bias in the mean percentage error as a result of increases or decreases of the individual variables.

4.1.1.5 Results

The mean percentage error (presented as a percentage of the expected value) for the $\dot{V}O_2$ and $\dot{V}CO_2$ values obtained during the tests are shown in *Figure 4.2*. Within the anticipated patient flow range (30-90 L.min^{-1}), there was <10% error in $\dot{V}O_2$ values when compared to those expected. However, there was up to a 15% error between expected and obtained values for $\dot{V}CO_2$.

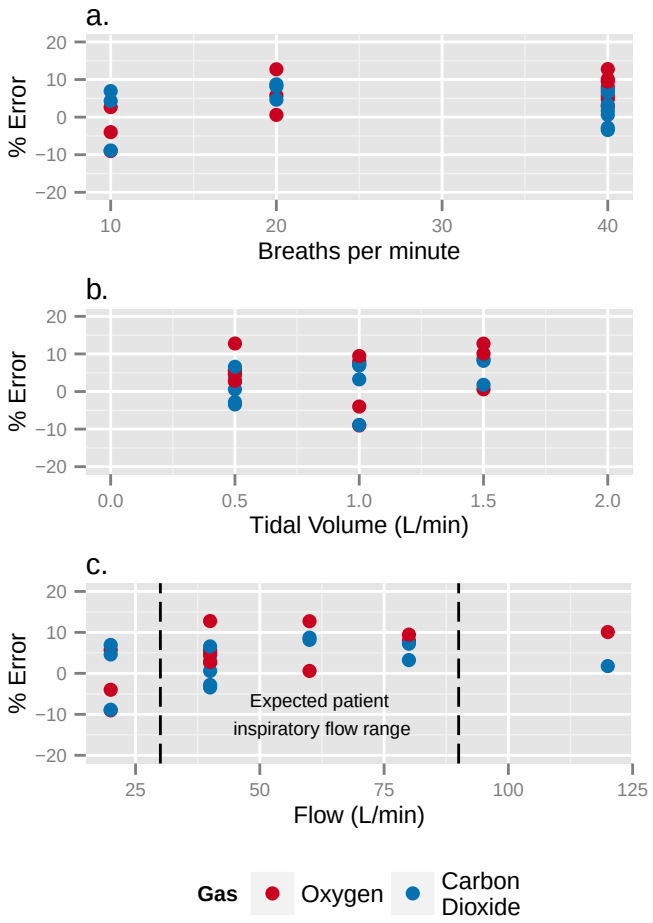


Figure 4.2: Percentage $\dot{V}O_2$ and $\dot{V}CO_2$ error for (a). respiratory rate (bpm), (b). tidal volume (V_T) and (c). inspiratory flow (L.min^{-1}). The potential peak inspiratory flow range for mechanically ventilated patients (30-90 L.min^{-1}) is illustrated.

4.1.1.6 Discussion

The developers of the GESV expect a intrinsic ± 2% error from the device itself and an additional ± 1% for flow and gas concentration error. In line with this, the American College of Chest Physicians suggest 3% accuracy should be maintained for exercise testing in non-ventilated patients [230]. Most, if not all BBGEA systems (and the GSEV devices used to test them), have been developed for exercise testing in athletes who generate $\dot{V}_E$ ≥100 L.min^{-1}, i.e. considerably greater than the <20 L.min^{-1} $\dot{V}_E$ anticipated for patients.

4.1.1.7 Conclusion

While relatively straightforward to provide *in vitro* validation of such devices, *in vivo* validation techniques lack a standard, accurate reference tool. However, *in vivo* validation is essential as mechanical ventilation introduces significant inconsistencies.

4.1.2 MGU flow sensor placement

During the process of familiarisation with the MGU, I observed that placing the flow sensor on the ventilator side of the the heat moisture exchanger (HME)[2] resulted in a 20-45% reduction in values obtained for both $\dot{V}CO_2$ and $\dot{V}O_2$, *(Figure 4.4 and Table 4.4)*. Two plausible explanations for the discrepancy were;

i) the way the device handles the different conditions the gas is exposed to, resulting in mis-representation of gas volumes. The HME removes water vapour from exhalate. Therefore, if the flow sensor was placed on the ventilator side *(Figure 4.3b)* rather than the patient side *(Figure 4.3a)* of the HME, the gas would be closer to ambient temperature and not fully saturated i.e. a smaller volume. If, however, the flow sensor were placed on the patient side of the HME then the gas would be closer to Body Temperature and Pressure, fully Saturated (BTPS), i.e. a larger volume.

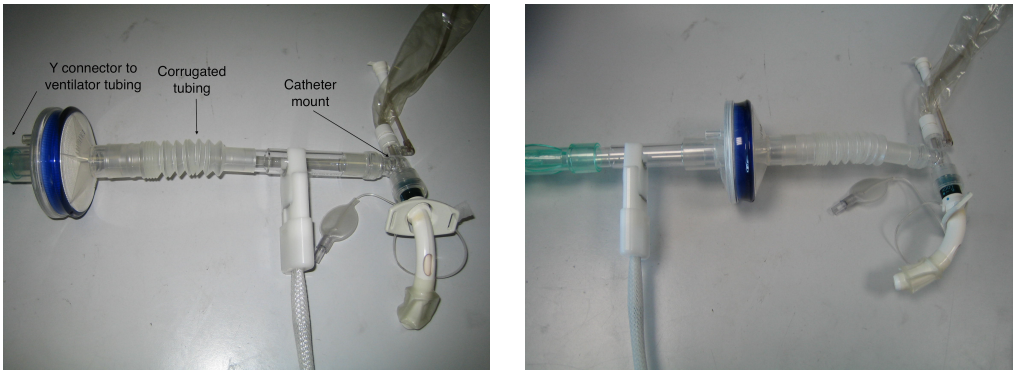
ii) the extra dead space created by the catheter mount and the HME may be altering the phase alignment of the gases *(Figure 3.1)*.

The following observations were carried out as figure *(Figure 4.5)*.

4.1.2.1 Objective

To establish if the difference in $\dot{V}CO_2$ and $\dot{V}O_2$ when the flow sensor was placed on the patient or ventilator side of the HME was due to misrepresentation of gas volumes.

[2]HME, a device used to humidify the patient's breathing circuit, which exchanges the heat and moisture in expired gas with the dry cold gas delivered by the ventilator.



(a) Flow sensor on the patient side of the HME. (b) flow sensor on the ventilator side of the HME.

Figure 4.3: Different positions of the MGU flow sensor.

4.1.2.2 Method

The MGU was set up and calibrated in-line with the manufacturer's instructions. Repeated tests were carried out on five additional patients with the flow sensor placed on the patient side of the HME *(Figure 4.3a)* and then with the device placed on the ventilator side of the HME *(Figure 4.3b)*. Breath-by-breath V_T data were downloaded from the patient's Servo-i ventilator (Maquet, Solna, Sweden). The Servo-i presents gas as ambient temperature and pressure saturated at 21℃ (ATP21). The Servo-i data was then time-aligned with the MGU V_T data which were presented as either body temperature pressure saturated (BTPS) or ambient temperature pressure saturated (ATPS). Resulting in five sets of data per patient.

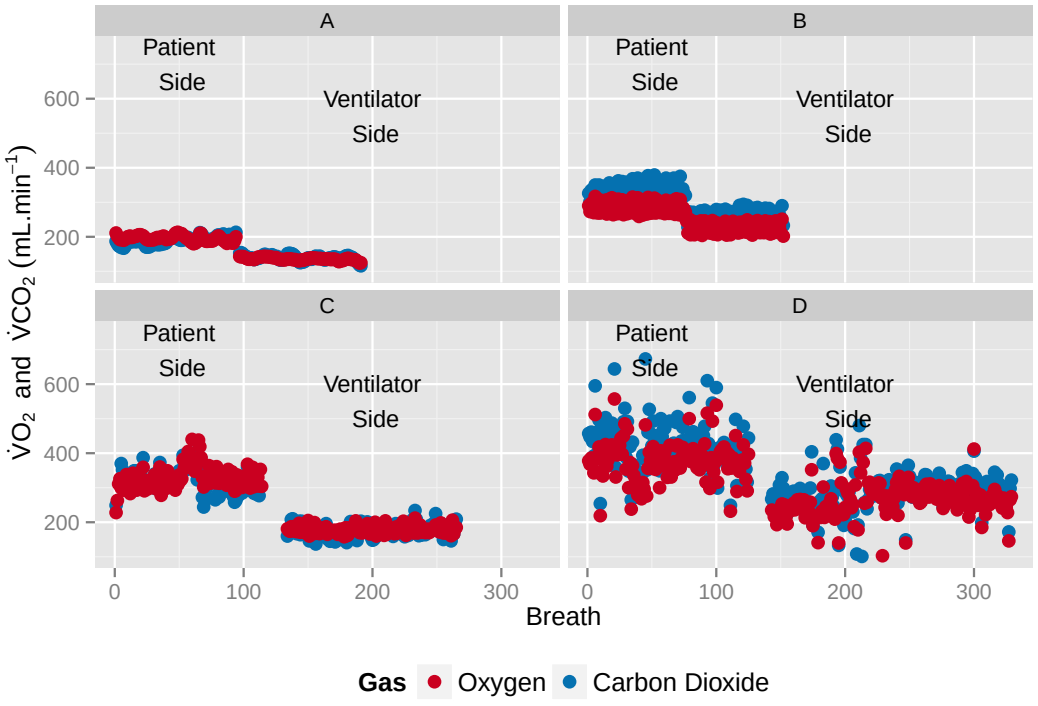


Figure 4.4: $\dot{V}O_2$ and $\dot{V}CO_2$ with changing the placement of the MGU flow sensor.

Patient	$\dot{V}CO_2$			$\dot{V}O_2$		
	VS	PS	% difference	VS	PS	% difference
A	135	195	30.77	139	189	26.46
B	227	286	20.63	256	334	23.35
C	178	326	45.40	175	319	45.14
D	263	377	30.24	287	427	32.79

Table 4.4: $\dot{V}CO_2$ and $\dot{V}O_2$ values on changing the location of the MGU flow sensor. VS = flow sensor ventilator side of HME, PS = flow sensor ventilator side of HME.

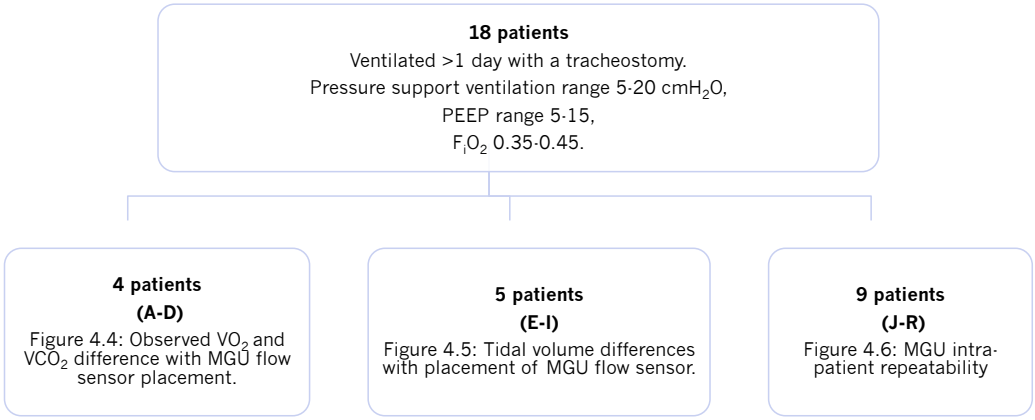


Figure 4.5: Consort diagram for MGU pre-validation observations.

4.1.2.3 Results

Tidal volumes with the flow sensor on the patient side of the HME were consistently greater than those when the flow sensor was on the ventilator side of the HME (*Figure 4.5 and Table 4.5*).

4.1.2.4 Discussion

In four of the five patients studied the variation in V_T did not account for the total discrepancy in $\dot{V}CO_2$ and $\dot{V}O_2$ values. Subsequent consultation with MedGraphics recommended flow sensor placement on the patient side of the HME. Consideration must then be given to the conditions the gas is exposed to, with both HME and humidified Fisher Paykel circuits (which warm and humidify inspired gas using a heated water bath). Additionally, the dead-space before and after the flow sensor must be accounted for. Internal dead-space refers to the distance between the sampling line and the patient. This volume only affects the dead-space calculations ($\dot{V}_E$ / $\dot{V}CO_2$ and $\dot{V}_E$ / $\dot{V}O_2$) made by the *Breeze Suite* software when it corrects

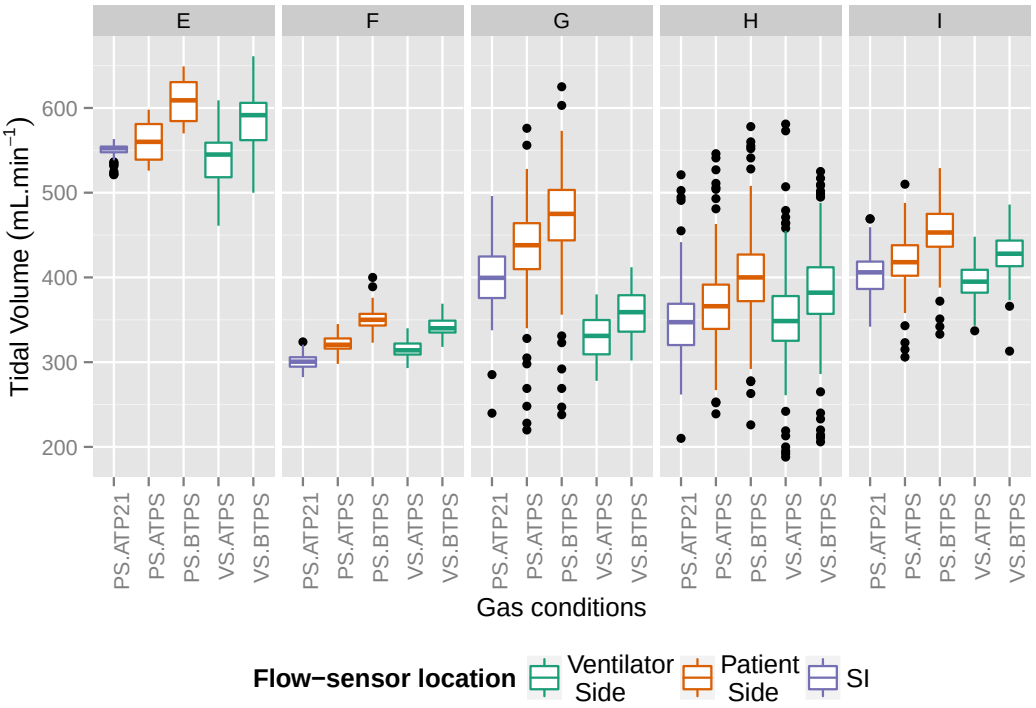


Figure 4.6: Tidal volume differences with placement of MGU flow sensor the patient side (PS) and the ventilator side (VS) of the HME. Each panel is one patient.

Patient	ATP21 PS.ATPS % difference	PS-VS BTPS % difference	PS-VS ATPS % difference
E	-1.76	3.54	3.50
F	-7.12	2.53	2.11
G	-7.96	23.86	23.87
H	-3.78	4.28	4.36
I	-3.33	5.78	5.60

Table 4.5: Percentage difference in $\dot{V}_T$ with the flow sensor in different positions. PS = flow sensor patient side of the HME, VS = flow sensor ventilator side of the HME.

for dead-space. External or mechanical dead-space is the distance from the sampling line to the ventilator circuit and has a considerable impact. The dead-spaces of the respective circuits were obtained by filling them with water and weighing them. Values are shown in *Table 4.6*. Of interest, the Servo-i[3] delivers a breath 10-20% larger than most clinicians would expect *(Table 4.7)*.

4.1.2.5 Conclusion

The flow sensor should be placed the patient side of the HME.

Circuit type	Dead-space after flow sensor (mL)	Relative humidity (%)	Temperature (℃)
Fisher Paykel (Heated Humidifier)	44	75	37
Dar (HME)	80	83	35
Pall (HME)	60	83	30

Table 4.6: Environmental conditions for the MGU.

Patient	E	F	G	H	I
MGU.BTPS Mean V_T (mL)	608	351	469	396	453
SI.ATP21 Mean V_T (mL)	550	301	357	355	404
% difference	10	17	11	12	12

Table 4.7: V_T differences when changing how the data is presented; SI.ATP21 (Ambient Temperature and Pressure Saturated at 21°C reported by the Servo-i) and MGU.BTPS (Body Temperature and Pressure Saturated, measured by the MGU).

4.1.3 MGU intra-patient repeatability

At a very basic level, within patient repeatability would give an indicator of the system precision. These repeatability tests were performed recognising that patients' metabolic demands are not stable over time.

[3]The specifications of the Servo-i are ± 7% for V_T [231].

4.1.3.1 Objective

To investigate the repeatability of the VO_2, VCO_2, V_E, RQ and resting energy expenditure (REE) measurements.

4.1.3.2 Method

Repeated tests were carried out in an additional nine mechanically ventilated patients. The MGU was set up and calibrated in line with the manufacturers instructions. Up to 3 tests for each patient were carried out within a single data collection session. Each test ran until 10 minutes of steady state data was obtained. Steady state was defined as a within test covariance <10% of $\dot{V}O_2$ and $\dot{V}CO_2$. The MGU was recalibrated prior to each individual test.

4.1.3.3 Analysis

Coefficients of variation (COV)[4] were calculated for REE, RQ, $\dot{V}_E$, $\dot{V}O_2$ and $\dot{V}CO_2$.

4.1.3.4 Results

The coefficients of variation for $\dot{V}O_2$,$\dot{V}CO_2$,$\dot{V}_E$, REE, and the RQ are displayed in *Tables 4.8a-e*. Graphical representation is given in *Figure 4.6*. Greater variation was seen in the $\dot{V}O_2$ values compared to the $\dot{V}CO_2$ values.

4.1.3.5 Discussion

Seven of nine completed tests demonstrated good repeatability (COV <4%). The remaining two tests demonstrated COV of <14%.

4.1.3.6 Conclusion

Repeatability was grossly demonstrated to be acceptable within the limits of patient stability.

4.2 Reference device calibration studies

4.2.1 Douglas bag collections

Douglas bag collections and the calculations required for subjects breathing room air are relatively straightforward. When the subject is receiving mechanical ventilation, calculation of $\dot{V}O_2$ and $\dot{V}CO_2$ from the expired gas requires that both F_iO_2 and flow-by are taken into account. Flow-by effectively adds (in the case of the Servo-i) 2 $L.min^{-1}$ of the gas the patient is breathing. The formulae for calculating $\dot{V}O_2$ and $\dot{V}CO_2$ in mechanically ventilated patients

[4] COV = standard deviation/mean*100

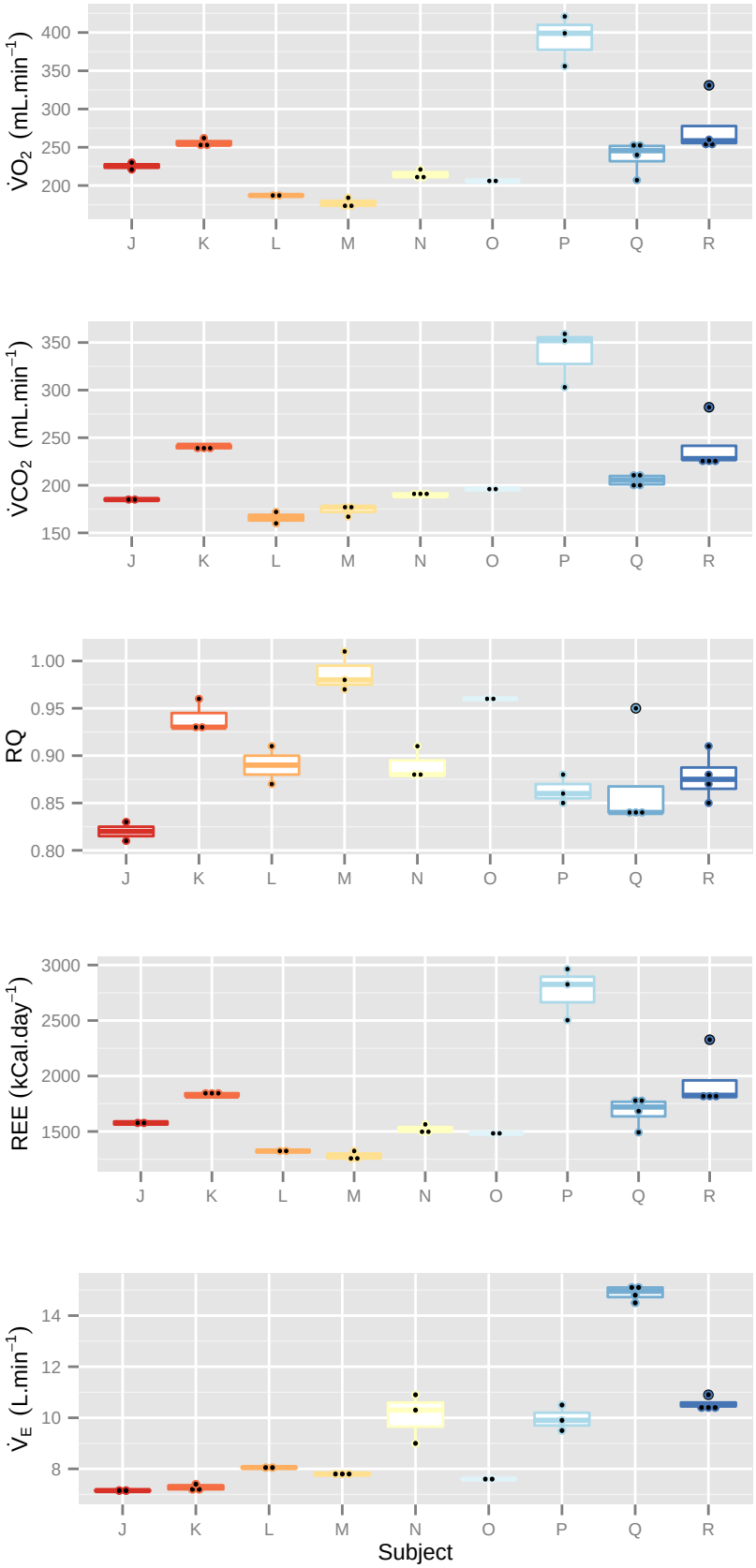


Figure 4.7: MGU Intra-patient repeatability (a).$\dot{V}O_2$, (b).$\dot{V}CO_2$, (c).RQ, (d).REE. Each coloured circle is an individual metabolic test.

Subject	$\dot{V}O_2$ (mL.min^{-1})		COV
	Mean	SD	(%)
J	225.50	6.36	2.82
K	256.00	5.29	2.07
L	187.00	2.83	1.51
M	177.00	6.56	3.70
N	214.33	6.51	3.04
O	206.00	1.41	0.69
P	392.00	33.06	8.43
Q	238.00	21.53	9.04
R	274.75	37.69	13.72

(a) $\dot{V}O_2$

Subject	$\dot{V}CO_2$ (mL.min^{-1})		COV
	Mean	SD	(%)
J	185.00	2.83	1.53
K	240.00	3.46	1.44
L	166.00	8.49	5.11
M	173.67	5.77	3.32
N	190.33	3.21	1.69
O	196.00	1.41	0.72
P	338.00	30.51	9.03
Q	205.25	6.40	3.12
R	240.25	27.93	11.63

(b) $\dot{V}CO_2$

Subject	RQ		COV
	Mean	SD	(%)
J	0.82	0.01	1.72
K	0.94	0.02	1.84
L	0.89	0.03	3.18
M	0.99	0.02	2.11
N	0.89	0.02	1.95
O	0.96	0.00	0.00
P	0.86	0.02	1.77
Q	0.87	0.05	6.34
R	0.88	0.02	2.85

(c) RQ

Subject	$\dot{V}_E$ (L.min^{-1})		COV
	Mean	SD	(%)
J	7.15	0.07	0.99
K	7.27	0.15	2.10
L	8.05	0.07	0.88
M	7.80	0.10	1.28
N	10.07	0.97	9.65
O	7.60	0.00	0.00
P	9.97	0.50	5.05
Q	14.88	0.29	1.93
R	10.55	0.25	2.39

(d) $\dot{V}_E$

Subject	REE (kCal/day)		COV
	Mean	SD	(%)
J	1577.00	39.60	2.51
K	1835	30.62	1.67
L	1324	28.28	2.14
M	1279	44.00	3.44
N	1519	42.19	2.78
O	1483	11.31	0.76
P	2764	236.61	8.56
Q	1683	135.91	8.08
R	1944	255.70	13.15

(e) REE

Table 4.8: Coefficients of variation for intra-patient reliability.

are given in *Appendices A.3*. These formulae have been adapted from measurements in individuals breathing room air [232].

The potential sources of error and the subsequent impact on $\dot{V}O_2$ and $\dot{V}CO_2$ are given in *Table 4.9*. In order to minimise these errors, I carried out a series of calibration tests of the aspects that were potentially controllable. i.e. mixing of expired gas with room air when sampling the gas, the accuracy of the gas analyser, the accuracy of the Harvard dry gas meter and the relative humidity of the expired gas.

Source of error	$\dot{V}O_2$ mL.min^{-1}(%)	$\dot{V}CO_2$ mL.min^{-1}(%)	RQ
0.1 Kpa increase in F_e0_2	-16.42 (-6.67)	0	-0.05
0.1 Kpa increase in F_eC0_2	-5.34 (-2.17)	12.45 (7.11)	0.07
1 L increase in $\dot{V}_E$	4.09 (1.66)	2.91 (1.66)	0
5% increase in humidity	-0.62 (-0.25)	-0.44 (-0.25)	0
0.1% increase in F_i0_2	15.79 (6.41)	0	-0.08
0.5℃ increase in temperature	-1.43 (-0.58)	-0.29 (-0.17)	0.00

Table 4.9: Potential sources of error associated with Douglas bag calculations.

4.2.1.1 Evaluation of gas sampling from the Douglas bags using a 3-way tap and syringe

Objective. To establish the extent of contamination of sampled gas with room air when extracting a gas sample from the Douglas Bag using a 50 mL Luer-lock syringe and 3-way-tap.

Method. A 5% CO_2, 55% O_2, balanced N_2 precision gas was used(General Electric, Bucks, UK).

Sample 1: Forty mL of precision gas was drawn into a 50 mL Luer lock syringe through a 3-way-tap without purging either the syringe or the tap. This was then analysed with an ABL735 Radiometer Blood Gas Analyser (NNU).

Sample 2: The 50 mL Luer lock syringe and 3-way tap were purged with sample gas and then 40 mL was drawn into the syringe. This was then analysed with the ABL735 Radiometer (NNU).

Sample 3: The same procedure as sample 2, but the sample was analysed using the ABL735 Radiometer (A/E).

Results. There was significant dilution of the expired gas with room air if the syringe and 3-way tap were not purged with expired gas from the Douglas Bags (*Table 4.10*).

Sample	O_2		CO_2	
	Fraction	%	Fraction	%
1. Unpurged (NNU)	49.6	52.4	4.18	4.4
2. Purged (NNU)	52.8	55.8	4.62	4.9
3. Purged (A/E)	53.2	55.7	4.62	4.8

Table 4.10: Gas concentrations with purged and unpurged syringe.

Discussion. There was evidence of mixing of the precision gases when the 3-way tap and syringe were not purged. There was a 3.2-3.6 kPa and a 0.42 kPa difference between purged and unpurged O_2 and CO_2 samples, respectively. Given a 0.1 kPa error in the F_eO_2 would result in a 6.67% change in $\dot{V}O_2$ and a 0.1 kPa error in F_eCO_2 would result in a 2% $\dot{V}O_2$ and 7% $\dot{V}CO_2$ error, this needed to be controlled.

Conclusion. The 3-way tap and syringe must be purged with expired gas prior to gas sampling.

4.2.1.2 Calibration of the Radiometer blood gas analysers

The accuracy of the gas sampling analysis is integral to the accuracy of the Douglas bag collection (DBC) technique.

Objective. To establish if calibration equations were required for the Radiometer blood gas analysers used for the DBC gas analysis.

Method. Four, 50 mL samples of the two precision gases (5% CO_2 and 55% O_2, balanced N_2 (General Electric, Amersham, UK) and 1.5% CO_2 and 21% O_2, balanced N_2 (BOC, Windlesham, UK)) were analysed using two Radiometer blood gas analysers. Two gas analysers were used as the NNU735 broke part way through the study and was replaced by the NNU835.

Results. At 21.273 kPa and 56.045 kPa O_2 (test gas) there was a 1.473 to 1.491 kPa and 2.845 to 2.795 kPa difference. At 1.521 kPa and 5.045 kPa CO_2 (test gas) there was a -0.039 to -0.2095 kPa and a 0.4 kPa difference for CO_2. The % differences are given in *Table 4.11.*

Sample	Device	Precision Gas (%)	Measured value (%)
1	NNU7	5	5.90
2	NNU7	55	57.91
3	NNU8	5	6.14
4	NNU8	55	57.87

(a) O_2

Sample	Device	Precision Gas (%)	Measured value (%)
1	NNU7	1.50	1.58
2	NNU7	21.00	23.30
3	NNU8	1.50	1.52
4	NNU8	21.00	23.37

(b) CO_2

Table 4.11: Precision gas results

Discussion. Given the potential impact of inaccuracy of the ABG machine gas measurements, calibration equations were required for the gas machines.

Conclusion. Equations were generated to provide calibration factors for CO_2 and O_2 for each machine. *(Figure 4.7).*

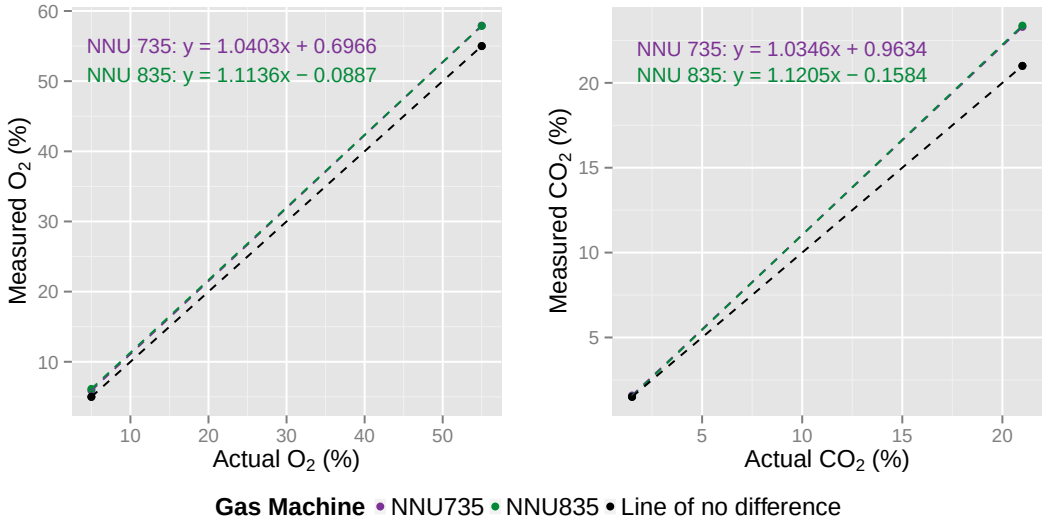


Figure 4.8: Gas machine calibration equations.

4.2.1.3 Harvard dry gas meter

A Harvard dry gas meter (HDGM) was used to measure the expiratory gas volume collected in the Douglas bags. The gas meter requires a low flow vacuum to draw the gas through the meter. The company claim that it is accurate to 1.5% [233]

Objective. To establish the accuracy of the HDGM, assuming the accuracy of the MGU flow sensor.

Method. The flow sensor for the MGU was attached to the inlet of the HDGM and the HDGM joined to the low-flow wall vacuum unit. The low-flow suction was titrated to created

a flow of 0.25 L.min^{-1}. Suction was applied until the DGM registered that 50 L had been drawn through the device.

Results. Across the four tests the HDGM gave volumes that were within 2% of the expected value (*Table 4.12*).

Test	HDGM (L)	MGU (L) (ATPS)	Error (%)
1	50	49	2
2	50	49.5	1
3	50	49.5	1
4	50	49	2

Table 4.12: Precision of the Harvard dry gas meter with respect to the MGU flow sensor.

Discussion. The precision of this device would only have a 1-2% per L impact on the final $\dot{V}O_2$ and $\dot{V}CO_2$ values.

Conclusion. I decided not to include a correction for the HDGM.

4.2.2 Deltatrac II calibration tests

As described previously, the Deltatrac II (DTII) calculates $\dot{V}CO_2$ by measuring CO_2 concentration by a flow dilution technique. The accuracy of the system's flow generator is imperative. This requires regular calibration, and the flow settings to be changed appropriately.

4.2.2.1 Flow calculations

1g of Ethanol produce 0.973 litres of CO_2.

5 mL of pure Ethanol produces 3820 mL of CO_2.

If the Ethanol concentration is 99.7%, then

$$\frac{99.7}{100} * 3820 = 3808.54 \text{ mL of } CO_2 \text{ is produced.}$$

The total $\dot{V}CO_2$ produced during the test is calculated by summing all $\dot{V}CO_2$ values. The new flow will be

$$\frac{3808.54}{total\ \dot{V}CO_2\ (in\ mL)} * \text{old flow}$$

Objective. Calibration of the DTII flow generator.

Method.

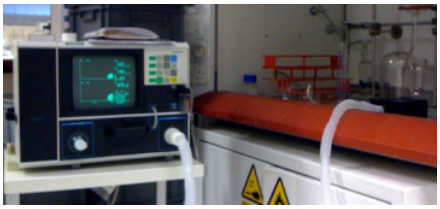
i) The DTII was warmed up for 30 minutes and the pressure and gas calibrations performed. The tests were run in canopy mode, with averaging and artefact suppression turned off.

ii) The set-up was prepared as in *Figure 4.8a*, with the alcohol burn kit within a fume hood.

iii) The alcohol burner vessel was filled with 5 mL of 99.7-100% Ethanol (*Figure 4.8b, Figure 4.8c, component 4*).

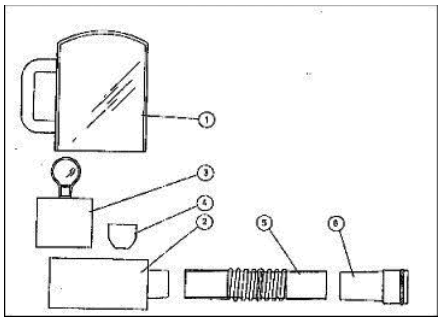
iv) The test was started, the alcohol ignited 30 sec later and the cover placed over the top of the burner *(Figure 4.8b, component 1).*

v) The test was run until the flame was extinguished. $\dot{V}CO_2$ values were recorded from the DTII until they reached 10 mL.min^{-1} when the test was stopped.



(a) DTII flow and RQ calibration set up.

(b) Alcohol burn kit.



(c) Alcohol burn kit schematic. Burner cover (1), Wick (2), Base (3), Burner vessel (4), Deltatrac Attachment(5/6).

Figure 4.9: Laboratory DTII calibration set up.

The first seven flow calibration tests were carried out with the incorrect set-up of the testing equipment. The corrections made were for the size of the burner receptacle and the plug removed from the base to allow sufficient flow of clean air through the system.

Results. The recorded values are given in *Appendix A.2.* The sum of the $\dot{V}CO_2$ values was 3684 mL.

4.2.2.2 New flow calculation

$$\text{Old flow value} = 36.2\ L.min^{-1}$$

$$\frac{3808.54}{3684} = 1.03$$

$$1.03 * 36.2 = 37.3$$

Conclusion. The new flow setting was 37.3 L.min^{-1}

4.2.2.3 Respiratory Quotient Test

To check that the flow setting is acceptable, the RQ of a known chemical compound such as Ethanol should be measured.

The RQ of $C_2H_5OH + 3O_2 = 2CO_2 + 3H_2O$

$$\frac{\dot{V}CO_2}{\dot{V}O_2} = \frac{2}{3} = 0.67$$

(The average RQ from the last 15 minutes of the test should be between 0.64 - 0.69.)

(As steps $i - ii$)

iii) The set up was prepared as *Figure 4.8a*, with the alcohol burn kit within the fume hood. The alcohol burner *(Figure 4.8b, component 3)* was filled with 10 mL of 99.7-100% Ethanol. The alcohol was ignited and the glass placed over the burner *(Figure 4.8b component 1)*.

iv) The test was carried out for 30 minutes recording the RQ each minute *(Appendix A.2)*.

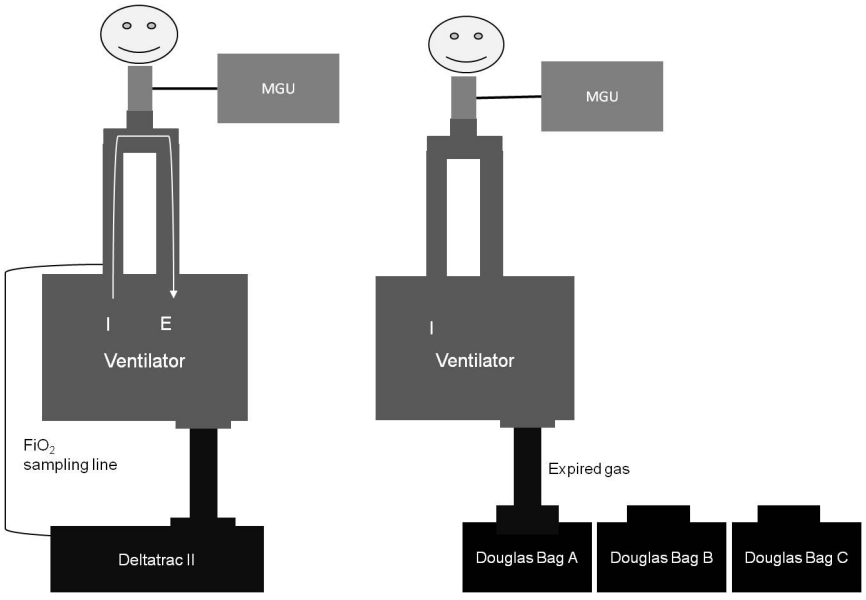
Results. The average of the last 15 RQ values was 0.67.

Conclusion. The new flow setting was acceptable.

4.3 Clinical comparison of the MedGraphics Ultima with Douglas bag collections and the Deltatrac II

4.3.1 Method

Ethical approval was granted for the study (REC reference number: 09/H1307/107) and informed consent or surrogate approval obtained from all patients or their next-of-kin. Patients mechanically ventilated on stable settings were recruited from the ICU at University College Hospital, London. Patients were excluded if they had burns, endotracheal or tracheal leaks >10%, open chest drainage, an inspired oxygen $F_iO_2 \geq 0.6$, were pregnant, <18 years of age, or had cardiorespiratory instability requiring frequent changes in ventilator settings, F_iO_2, inotropic or sedative drug dosages. The measurements were taken simultaneously therefore factors such as room temperature and nutritional status were not controlled. The mechanical ventilator used in all studies was the Servo-i (Maquet, Solna, Sweden). Before each test the DTII and MGU machines were warmed up for 30 minutes and calibrated in line with the manufacturers' instructions. Patients were clinically stable for 30 minutes preceding measurement (<20% variation in heart rate, blood pressure or oxygen saturation). Mechanical ventilation settings were kept stable over the hour preceding and during the test period. Oxygen consumption ($\dot{V}O_2$) carbon dioxide production ($\dot{V}CO_2$), REE, RQ were recorded breath-by-breath by the MGU over a 30-75 minute period. During this time simultaneous measurements were taken using the DTII and/or the Douglas bag. The tests were repeated, where possible, at different time points over the subsequent month to collect up to three paired measurements per patient using both MGU and DTII, and MGU and Douglas bag collection techniques *(Figure 4.9)*.



(a) MGU DTII Schematic. (b) MGU and DDBC schematic

Figure 4.10: Schematics of expired gas collection and measurement.

4.3.1.1 Douglas bag collection

For the current study, gas was collected over three five-minute periods from the expiratory exhaust of the ventilator, into separate pre-labelled 100 litre PVC gas collection bags (Harvard Apparatus Ltd, Edenbridge, UK). Pre-labelled 50 mL syringes and three-way taps were purged with 100 mL of expired gas from the respective gas collection bags, prior to aspiration of 50 mL of gas for analysis from each bag. Twenty mL of this gas was then analysed using a blood gas analyser (ABL735 or 825, Radiometer, Brønshøj, Denmark). Two precision gases; 5% CO_2 / 55% O_2 (General Electric, Amersham, UK) and 1.5% CO_2 / 21% O_2 balanced with N_2 (BOC, Windlesham, UK) were used to create reference equations for the gas analysers before the study began. The gas collection bags were emptied using a wall-mounted suction unit set at low flow, through a Harvard dry gas meter (Harvard Apparatus, Holliston, USA) calibrated at the beginning of the study. $\dot{V}O_2$, $\dot{V}CO_2$ and REE of the Douglas bags were then calculated *(Appendix A.3) (Figure 4.10).*

(a) Douglas bag attachment to the Servo-i.

(b) Douglas bags.

(c) Douglas bag exchange valves.

Figure 4.11: Douglas bag collections.

4.3.1.2 Deltatrac II

The mean of the values obtained over the first five-minute period where the coefficients of variation of both $\dot{V}CO_2$ and $\dot{V}O_2$ were $\leq$5% was used in the analysis [234–236].

4.3.1.3 MedGraphics Ultima

The flow sensor was calibrated using a 3 L syringe and the gas analysers calibrated with precision gas before each individual test. Data points within the MGU tests were excluded if the RQ was <0.6 or >1.2, the V_T was <150 mL, or the $\dot{V}O_2$ or $\dot{V}CO_2$ were <50 mL.min^{-1}. Collected data were then averaged as the middle five of seven breaths.

4.3.2 Analysis

Simultaneous MGU recordings were used for comparison against both DTII and Douglas Bag measurements. Measurements were discarded if the mean RQ value obtained from either the five minute DTII or the three Douglas bag collections were <0.6 or >1.2. Data were excluded if the coefficient of variation was >10% for individual Douglas bag collection or >5% for the DTII tests. All coefficients of variation for the MGU tests were <14%. Bland Altman plots (mean measurements made by the two devices vs. the difference in measurements between the devices) were used to calculate precision and bias. I decided *a priori* that a 30% error was acceptable, as recommended by Critchley and Critchley [237].

4.3.3 Results

Sixteen patients were recruited and tested on 39 occasions. Patient characteristics and ventilator settings for each test are given in *Table 4.13*. Comparisons between techniques, number of tests performed and proportion of excluded tests are shown in *Table 4.14*, while the reliability of the individual techniques is shown in *Table 4.15*. Bland Altman plots of $\dot{V}O_2$, $\dot{V}CO_2$, REE and scatter plots for RQ are presented in *Figure 4.11*, with bias and precision (95% limits of agreement) shown in *Table 4.16*.

4.3.3.1 MedGraphics Ultima (MGU) vs. Douglas Bag

Nineteen valid tests were carried out in ten patients. Although bias was good for $\dot{V}O_2$, $\dot{V}CO_2$ and REE, precision was weak with wide levels of agreement and a maximum random error of 54% for $\dot{V}O_2$, 51% for $\dot{V}CO_2$ and 43% for REE. If proportionality of the measurements is taken into account and the percentage error for each individual dataset calculated, then the random error is 42% (-27-15%) for $\dot{V}O_2$, 57% (-17-40%) for $\dot{V}CO_2$ and 32% (-9-23%) for REE (Appendix A.5).

4.3.3.2 MedGraphics Ultima (MGU) vs. Deltatrac II

Nineteen valid tests were carried out in nine patients. Overall bias was good for $\dot{V}O_2$, $\dot{V}CO_2$ and REE however, yet again, there were wide limits of agreement for all three measures. It was superior to the comparison between MGU and the Douglas bag techniques with random errors of 33%, 27%, and 31% for $\dot{V}O_2$, $\dot{V}CO_2$ and REE, respectively. If proportionality of measurements is taken into account, and the percentage error for each dataset calculated, then the random error widens to 41% (-13 to 28%) for $\dot{V}O_2$, 31% (2 to 29%) for $\dot{V}CO_2$, and 37% (-28% to 9%) for REE (Appendix A.5).

Patient	Test	Reason for admission	Age	BMI	Gender	Pressure support	PEEP	F_iO_2
1	1	Abdominal Aortic Aneurysm Repair	82	29	M	12	5	0.35
	2					12	5	0.40
2	1	Pneumonia	45	14	F	9	2	0.35
3	1	Gastric resection	79	25.7	F	5	5	0.40
	2					12	5	0.45
	3					12	5	0.45
3	1	Pneumonia	70	30	M	NAVA	5	0.30
	2							
	3							
5	1	Pneumonia	71	20	M	13	5	0.25
	2							
6	1	Coronary artery bypass graft	78	-	M	12	10	0.50
	2					12	10	0.55
	3					6	10	0.45
7	1	Whipple's procedure	66	-	M	10	5	0.30
8	1	Hemicolectomy	75	21.7	F	13	5	0.35
	2					12	5	0.25
	3					10	5	0.30
9	1	Pancreatitis	79	27.7	M	10	5	0.25
	2					15	5	0.25
	3					0	0	0.28
10	1	Small bowel resection	79	19.7	F	5	5	0.28
	2					5	5	0.28
	3					5	5	0.30
11	1	Thrombotic thrombocytopenic purpura	58	35	F	10	5	0.30
	2					10	5	0.35
	3					0	5	0.35
12	1	Pleurodesis	76	34	M	8	5	0.30
13	1	Small bowel ischemia	69	-	F	14	5	0.35
	2					5	5	0.30
	3					0	5	0.30
14	1	Urosepsis and heart failure	74	-	F	20	5	0.40
	2					20	8	0.30
	3					15	5	0.30
15	1	Femoral artery aneurysm	69	-	M	0	5	0.25
	2					0	5	0.30
16	1	Pneumonia and heart failure	61	47.3	M	0	5	0.30
	2					0	5	0.30
	3					5	5	0.30

NAVA = neurally adjusted ventilatory assist. PEEP = positive end expiratory pressure.

Table 4.13: Patient characteristics

Comparison	Number of patients tested	Number of tests	Number of tests used	Reason for not using tests
MGU vs. DB	10	25	19	3 RQ errors with DB 3 COV errors of MGU
MGU vs. DTII	9	24	19	2 RQ errors and 1 COV error with DTII
TOTAL	16	39	35	4

RQ = Respiratory quotient, COV = Coefficient of variation.

Table 4.14: Distribution of tests across patients and why the tests were not used.

Technique	Unusable data	Reason why unusable
MGU	3/39 (7%)	Unstable $\dot{V}O_2$
DB	26/75 (34%)	19 RQ unacceptable
	of bags collected	6 volume loss from Douglas Bags,
		1 expiratory gas analysis error.
DTII	3/24 (12%) of tests	2 RQ unacceptable,
		1 COV error.

Table 4.15: Reliability of the individual techniques.

Comparison	Parameter	Mean	Bias	Precision	Maximum % error
MGU vs. DB	$\dot{V}O_2$	231	+7.0	-56 to +70	54
MGU vs. DTII	($mL.min^{-1}$)	272	-10.3	-56 to +35	33
MGU vs. DB	$\dot{V}CO_2$	208	+31	-22 to +85	51
MGU vs. DTII	($mL.min^{-1}$)	249	+34	-0.6 to +68	27
MGU vs. DB	REE	1655	+93	-263 to +449	43
MGU vs. DTII	($kCal.day^{-1}$)	1812	+28	-249 to +305	31

Table 4.16: Precision and bias for $\dot{V}O_2$ $\dot{V}CO_2$ and REE measurements made between the MedGraphics Ultima (MGU) Deltatrac II (DTII), and Douglas bag techniques. Maximum % error = $2SD/\mu$

4.3.4 Discussion

This study describes the unique comparison of a currently available device the MedGraphics Ultima (MGU) with traditional "reference standards", namely the Deltatrac II and the Douglas bag technique, in mechanically ventilated patients at rest. While the systematic error (bias) between the MedGraphics Ultima measurements of $\dot{V}O_2$, $\dot{V}CO_2$ and REE, and between those of the Deltatrac II and the Douglas bag, was acceptable, the limits of agreement were wide. Comparison between the MGU and the DTII was more acceptable but at the margins of acceptability for measurement of metabolic activity, either for research or clinical purposes, albeit assuming that the Deltratrac II represents an accurate gold standard.

Accepting that these reference devices have their limitations (see later), there is a remarkable lack of consistency in the criteria deciding comparability between a reference technique and new devices. Using cardiac output measurement techniques as an example, Critchley and Critchley [237] proposed that the accuracy of both devices should be taken into account. Thus if the reference device, in this case the DTII, was considered to have an accuracy of ± 20% and the test method, in this case the MGU, a similar accuracy, then the combined limits of agreement would be ± 28%.

The MedGraphics Ultima (MGU) is predominantly used in exercise testing in spontaneously breathing patients [238]. Validation for this device is relatively scanty, even in spontaneously breathing subjects. Cooper et al compared the MGU and four other devices against the DTII in resting subjects and found all were inferior in terms of within-patient coefficient of variation for resting metabolic rate, ranging from 4.8-10.9% compared to 3% for the DTII [239]. Other studies in healthy self-ventilating individuals using the MedGraphics CCM Express, a device similar to the MGU, have shown acceptable agreement, though lower absolute values compared to the reference technique [240, 241].

$\dot{V}O_2$ in mechanically ventilated patients at rest is relatively low (approximately 250 $mL.min^{-1}$), in comparison to the 2-5 $L.min^{-1}$ values seen at peak exercise in ambulant healthy individuals [242]. Therefore, the signal to noise ratio is far greater in resting mechanically ventilated patients than that recommended by the exercise testing literature [230].

Data directly validating indirect calorimetry devices in mechanically ventilated patients are also scarce, despite their promotion as a tool to titrate nutritional input. A recent study [243] in 24 ICU patients reported mean REE values as 64% higher for the CCM Express compared against the Deltratrac. Repeated readings from the same instrument gave a coef-

ficient of variation of 4.1% and 7.9% for Deltatrac and CCM Express, respectively. In the present study, I did not find a systematic bias, although limits of agreement were wide. The coefficients of variation for $\dot{V}O_2$ were <5% between each minute of the 5-minute test for the DT II, <10% between each bag in a single Douglas bag collection test and <14% for breath-to-breath measurements with the MGU. However, despite my measurements being taken at rest, the pattern of breathing of most patients was irregular. This may have contributed to the intra-device differences, in particular the MGU measures breath-by-breath and the DTII measures over 1 minute while the DB measurement is averaged over a 5 minute collection. This is consistent with the lack of bias but poor precision seen between techniques.

The accuracy of the reference standard must be taken into account. Tissot et al [221] directly compared the Deltatrac II with either Douglas bag gas collections or mass spectroscopy in 35 mechanically ventilated patients, and found both excellent bias and precision. On the other hand, Takala et al found $\dot{V}O_2$ values obtained from the Deltatrac were consistently higher than pulmonary artery catheter-obtained indirect Fick measurements in ICU patients following cardiac surgery [223]. These ranged from 16 ± 9% during controlled ventilation, 21 ± 8% during synchronized intermittent mandatory ventilation, to 25 ± 8% during spontaneous breathing. Levinson et al also found that $\dot{V}O_2$ measured by indirect calorimetry (using a Douglas bag and mass spectrometry) was 15% higher than that measured by thermodilution in 29 mechanically ventilated patients [224]. In part, this discrepancy may be related to lung oxygen consumption which is not measured by thermodilution and estimated to be 14 ± 3% of whole body $\dot{V}O_2$ [244]. Other studies also report inconsistent findings regarding the accuracy of newer devices compared against the DTII, e.g. the M-COVX device [225–227]. Many of these studies were performed using mechanical ventilators that did not use bias flow (flow-by). This is a continuous flow of gas, usually in the order of 2 $L.min^{-1}$ of the pre-set level of inspired O_2 that is incorporated into most, if not all, modern ventilators. Depending on the device being utilised for oxygen consumption, mishandling of this extra volume of oxygen added to the expired volume can significantly impact on the values obtained. Both the MGU and DTII are unaffected by bias flow; the MGU utilises a flow sensor sited at the endotracheal tube within the ventilator circuit while the DT II measures neither flow nor volume as part of its calculation technique. However, this is a potential source of error for Douglas bag collection or any other device that relies on expiratory volumes.

On the other hand, the dead-space created by ventilator tubing and heat moisture exchange systems must be adequately accounted for so that the MGU correctly phase aligns the flow, oxygen and carbon dioxide signals. For reliable measurements, scrupulous attention

needs to be paid to the performance of the different techniques, and awareness of the many potential pitfalls. For example, both the Douglas bag technique and indirect calorimetry have multiple potential sources of error *(Tables 4.1 and 4.9)*. While every attempt was made to control these errors during this study, the Bland Altman plots illustrate considerable random rather than systematic error. A 16% measurement error for $\dot{V}O_2$ is recognised for the Douglas bag technique [224].

I reduced the potential physiological variability of the tests by performing measurements simultaneously. The possibility that the sampling techniques bias each other was small. The DTII samples inspiratory gas continuously at 150 mL.min^{-1} against a $\dot{V}_E$ of 12 L.min^{-1} giving, at worst, a reduction of 1.25% of $\dot{V}_E$. The MGU samples gas continuously, both during inspiration and expiration, at a maximum of 130 mL.min^{-1}, potentially creating a 0.36% inspiratory volume error and a 0.72% expiratory volume error.

The accuracy of the F_iO_2 displayed by the Servo-i was not established at the beginning of the study. The manufacturer of the Servo-i specifies a ± 5% error from the displayed value. Subsequent investigation in five patients has found a mean ± SD of 0.58% ± 0.29% difference in the F_iO_2 displayed by the Servo-i and the MGU *(Table 4.17)*. This may have lead to considerable inaccuracies in the DB calculations.

Patient	Mean F_iO_2 % difference (Servo-i-MGU)	Standard Deviation of mean difference
A	0.64	0.07
B	0.55	0.29
C	0.66	0.25
D	0.35	0.06
E	0.71	0.33

Table 4.17: Percentage variation in Servo-i F_iO_2 reading.

As a clinical tool, changes in $\dot{V}O_2$ may be more relevant and reliable than absolute values, e.g. in response to a physiological challenge (e.g. sitting on edge of bed, change of ventilator settings). This study enrolled relatively low numbers of patients with a limited range of $\dot{V}O_2$, but it serves to highlight some of the issues and pitfalls that must be addressed in order to develop a metabolic monitoring device that is fit for purpose. Such a device needs to be integrated into a mechanical ventilator, accommodate the challenges of temperature, humidity, dead space, and tidal volume entropy and specifically have precision at low levels of $\dot{V}O_2$.

4.3.4.1 Potential tolerable errors of $\dot{V}O_2$ for exercise in mechanically ventilated patients

Assuming a 70 Kg person, in order to track change when used with;

1. unloaded cycling, $\dot{V}O_2$ for a 70 Kg person = 150 +(6*70)=570 mL.min^{-1}, with an expected $\Delta\dot{V}O_2$ of 10 mL.min^{-1}.watt^{-1}, i.e. 5 watts = 50 mL increase, 10 watts = 100 mL increase.
   Therefore the device would need to pick up a 50 mL $\dot{V}O_2$ change.

2. Lying to sitting = 3.5 mL.Kg^{-1}.min^{-1} (245 mL) to 4.25 mL.Kg^{-1}.min^{-1} (297.5 mL).
   Therefore the device would need to pick up a 53 mL $\dot{V}O_2$ change.

3. Sit to stand = 4.25 mL.Kg^{-1}.min^{-1} (297.5 mL) to 8.75 mL.Kg^{-1}.min^{-1} (612.5 mL).
   Therefore the device would need to pick up a 315 mL.min^{-1} $\dot{V}O_2$ change.

4. Standing to walking at 3mph = 8.75 mL.Kg^{-1}.min^{-1} (612.5ml) to 10.5 mL.Kg^{-1}.min^{-1}.
   Therefore the device would need to pick up a (735ml/min) a 123 mL.min^{-1} change.

4.3.5 Conclusion

Although showing low bias when compared to the reference methods of the Douglas bag technique and the Deltatrac II indirect calorimeter, the MGU lacks precision. This may be due, in part to limitations of the reference methods. For this field to move forward, industry must collaborate with clinicians and researchers to improve the accuracy of devices that monitor gas exchange in mechanically ventilated patients. Despite the limitations and complexity of the measurements, I decided that it would still be possible to identify a change in $\dot{V}O_2$ given that the expected increase in $\dot{V}O_2$, as a result of exercise, was greater than the limits of agreement of the MGU.

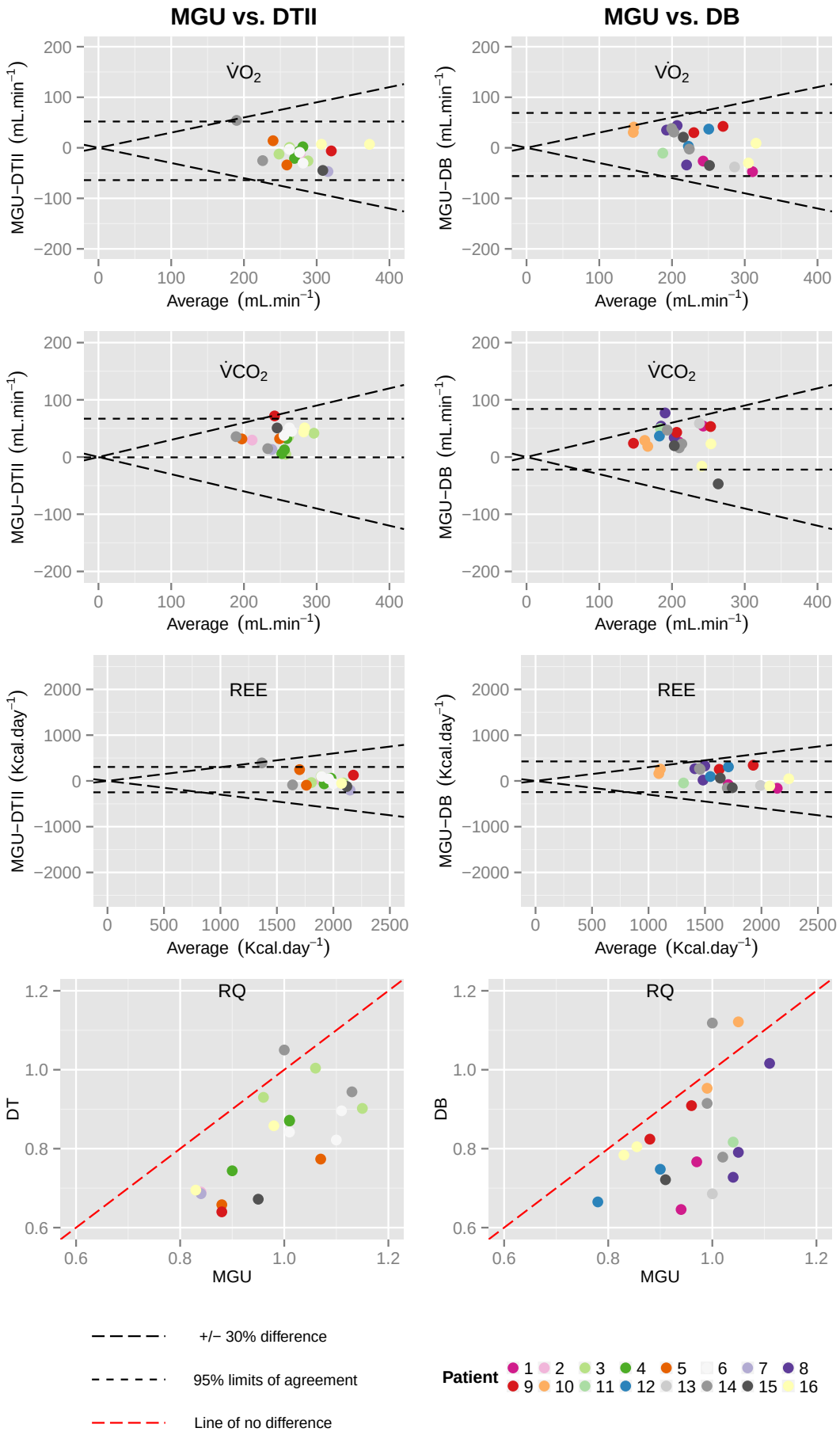


Figure 4.12: Bland Altman plots of $\dot{V}O_2$, $\dot{V}CO_2$ and REE, and RQ scatter plot.

Chapter 5

The feasibility of measuring oxygen consumption during rehabilitation interventions in mechanically ventilated patients

The next stage in establishing a method of measuring exercise intensity in mechanically ventilated patients was to ascertain if the MGU could track changes in $\dot{V}O_2$ during exercise. However, as there are currently no standardised exercise stimuli for mechanically ventilated patients, it was also necessary to evaluate the usefulness of different exercise stimuli in mechanically ventilated patients.

5.1 The properties required of physiologically and clinically useful measurement tools

Tools to measure exercise intensity and capacity in mechanically ventilated ICU patients require robust clinimetric properties [245]. As such the ideal tool should have concurrent and construct validity, that is it should measure what it is intended to measure. It should be able to generate data similar to that of a gold standard and also that of a tool measuring a similar construct. In this case, BBGEA would be the gold standard for measuring absolute exercise intensity. It would also be the gold standard for estimating relative exercise intensity and exercise capacity in either incremental or a series of constant load tests. The tool used would need to demonstrate intra-patient repeatability and would need to have the sensitivity

to respond to clinically important differences in exercise intensity and capacity. Ideally such a tool should respond in a linear manner, with minimal bias at low and high end of the exercise intensity and capacity range. It should also have a minimal floor and ceiling effect. The tool should also be user-friendly; acceptable both to patients and clinicians and have good intra-tester reliability.

A feasibility study "Quantifying exercise capacity and intensity in ICU" was therefore carried out to investigate the feasibility of measuring exercise capacity and intensity in mechanically ventilated patients recovering from critical illness. The primary objective was to investigate the feasibility of measuring exercise capacity and intensity using BBGEA during cycle arm ergometry in such patients. The secondary objectives were to characterise normal rehabilitation interventions in mechanically ventilated ICU patients and to provide data to inform sample size calculations for future studies validating measurement tools of exercise capacity and intensity.

5.2 Feasibility study

During the feasibility study, I aimed to observe patients three times in the first week and then twice a week for the following two weeks. I anticipated that all patients would be studied during normal rehabilitation on day 1 and undertake a constant load test on days three and five. Patients who completed three minutes of exercise on either days 3 or 5 would then be randomised to either continue the constant load test or to undertake a ramp test. Patients who did not complete three minutes of exercise on both day 3 and day 5 would continue with the constant load test. This was done to ensure that the incremental group did not become a self-selecting group of patients with potentially greater exercise capacity. Therefore three groups were created: (i) those unable to cycle $\geq$3 minutes and who only had constant load exercise; (ii) those who could cycle $\geq$3 minutes but remained in the constant load group; and (iii) those who could cycle $\geq$3 minutes and had incremental exercise. A 3 minute cut-off was chosen as an acceptable length of time to reach a steady state of $\dot{V}O_2$. This is the recommended duration of unloaded cycling at the beginning of an incremental test [246]. The study design is summarised in *Table 5.1.*

5.2.1 Anticipated recruitment and sample size calculation

Approximately eighty patients per year are ventilated for more than fourteen days on the ICU at UCH. The current recruitment rate of studies on the ICU is 50%. Therefore I anticipated that up to forty patients could be recruited in one year. It was expected that this design

would result in approximately equal number of patients in each of the three groups. It was anticipated that one third of patients randomised to cycling would not achieve 3 minutes of exercise on day 3 or on day 5 and the rest would be randomised on equal basis to either the constant load or ramp test from day 10. Thus, if 30 patients were recruited, there would be ten patients per group.

5.2.2 Outcomes

Primary outcomes.

i) Whether or not the patient was able to complete three minutes of constant load exercise at any time point.

ii) From incremental exercise: whether or not it was possible to identify the patient's anaerobic threshold from BBGEA using the V-slope method [246].

iii) From incremental exercise: whether or not it was possible to identify the patient's lactate threshold, taken as a sustained increase in blood serum lactate concentration.

Secondary outcomes. I aimed to collect the following during every constant load, ramp test and rehabilitation session:

i) peak $\dot{V}O_2$ ($mL.min^{-1}$)

ii) excess post-exercise oxygen consumption (mL)

iii) heart rate recovery ($bpm.min^{-1}$)

iv) peak lactate concentration ($mmol.L^{-1}$)

v) rate of perceived exertion using the Borg 6-20 ordinal scale

vi) heart rate variability (ms).

I aimed to collect the following during each incremental test:

vii) peak work rate (watts).

I aimed to calculate the following:

viii) the mean response time of $\dot{V}O_2$ uptake, from all constant load tests that achieved a steady-state.

ix) the mean $\dot{V}O_2$ ($mL.Kg.^{-1}min^{-1}$) of the session,

x) the total VO_2 (mL.Kg.$^{-1}$) for each level of rehabilitation achieved at each rehabilitation session,

xi) the relationship of $\dot{V}O_2$ (mL.min^{-1}) to HR bpm,

xii) the relationship of $\dot{V}O_2$ (mL.min^{-1}) to RPE,

xiii) the intra-patient reliability of the above values,

xiv) the sensitivity to change over time of the above values.

Ethical approval was granted for the study (REC reference number 11/LO/1646) and informed consent or surrogate approval was obtained from all patients or their next-of-kin. Patients were recruited from the intensive care unit at University College Hospital if they had been mechanically ventilated for over seven days via a tracheostomy, were adults aged 18 years or over, the patient or patient's representative was able to give informed consent/advice, and the patient was anticipated to be able to use an arm ergometer. I expected that some patients would be unable to use the ergometer in the very early stages of their rehabilitation. These patients were screened out, but could be included later on during their ICU admission. Patients were excluded if they were: aged under 18, mechanically ventilated via a tracheostomy for over seven days but still unable to use an ergometer on discharge from ICU, pregnant, unable to exercise due to pre-existing conditions or current morbidity; e.g. severe dementia, motor neurone disease, severe stroke, severe critical illness neuro-myopathy, moderate to severe stenotic valvular heart disease, primary pulmonary hypertension, hypertrophic cardiomyopathy, or unstable angina; or if the patient (or their representative) was unable to give informed consent or advice.

5.2.3 Methods and materials

Patients were assessed for suitability to exercise by the ICU physiotherapist, as per normal practice for the ICU *(Appendix B.1)*, before each exercise/rehabilitation session.

5.2.3.1 Normal rehabilitation sessions

Normal rehabilitation sessions consisted of sitting the patient over the edge of the bed, progressing the patient to standing, transferring and walking, as is normal practice in the ICU at UCLH. Exercise was terminated, if indicated, as it would be in normal clinical practice (*Appendix B.2*). Blood pressure was recorded from either an indwelling arterial cannula or using a non-invasive cuff. A Polar heart rate monitor and a MGU flow-sensor were attached to the patient's chest and ventilator circuit, respectively. The patient's ECG leads remained *in situ* throughout. To allow retrospective analysis of HR and $\dot{V}O_2$ for each activity, time points

<table>
<tr><td>Visit</td><td>Week</td><td>Day</td><td colspan="4">Patients recruited to study</td></tr>
<tr><td>1</td><td>1</td><td>1</td><td colspan="4">All normal rehabilitation</td></tr>
<tr><td>2</td><td>1</td><td>3</td><td colspan="2">Constant Load
Did not achieve 3 min exercise</td><td colspan="2">Constant Load
Did achieve 3 min exercise</td></tr>
<tr><td rowspan="3">3</td><td rowspan="3">1</td><td rowspan="3">5</td><td rowspan="2">Constant load.
Did not achieve
3 min</td><td>Constant load.
Did achieve
3 min</td><td>Constant load.
Did achieve
3 min</td><td>Constant load.
Did not achieve
3 min</td></tr>
<tr><td colspan="2">Randomised to constant load or ramp 1:1 ratio</td></tr>
<tr><td>Constant load
(Group 1)</td><td>Constant load
(Group 2)</td><td colspan="2">Ramp
(Group 3)</td></tr>
<tr><td>4</td><td>2</td><td>8</td><td>Normal
rehabilitation</td><td>Normal
rehabilitation</td><td colspan="2">Normal
rehabilitation</td></tr>
<tr><td>5</td><td>2</td><td>10 or 12</td><td>Constant load</td><td>Constant load</td><td colspan="2">Ramp</td></tr>
<tr><td>6</td><td>3</td><td>15</td><td>Normal
rehabilitation</td><td>Normal
rehabilitation</td><td colspan="2">Normal
rehabilitation</td></tr>
<tr><td>7</td><td>3</td><td>17 or 19</td><td>Constant load</td><td>Constant load</td><td colspan="2">Ramp</td></tr>
<tr><td>8</td><td>4</td><td>22</td><td>Normal
rehabilitation</td><td>Normal
rehabilitation</td><td colspan="2">Normal
rehabilitation</td></tr>
<tr><td colspan="3"></td><td>Cycling. Did
not achieve
3 min constant
load on day 3
or 5 Constant
load
throughout</td><td>Cycling. Did
not achieve
3 min constant
load on day 3.
Did achieve
3 min constant
load on day 5.
Constant load
throughout</td><td colspan="2">Achieved 3 min constant load
on visit 3 and 5. Ramp from
day 10 or 12</td></tr>
<tr><td colspan="3">Estimated number</td><td>10</td><td>10</td><td colspan="2">10</td></tr>
</table>

Table 5.1: Original protocol.

were recorded when the following activities were carried out: organising the bed space, process of SOEB, STS, standing, BCT, sitting in a chair, transferring from chair to bed, moving themselves horizontally up the bed, from sitting to lying and recovery.

5.2.3.2 Symptom-limited constant unloaded exercise test

Arterial/non-invasive blood pressure (ABP/NBP) measurements were recorded. A Polar heart rate monitor and MGU flow-sensor were attached to the patient. The patient was transferred into a chair through whatever means was normal for them, i.e. hoist, sliding, horizontal or standing transfer. Following the transfer, when $\dot{V}O_2$, $\dot{V}_E$ and HR had stabilized to within 10% of values at baseline, the patient was guided to cycle for 1 minute at 35 RPM. They were then asked to rest to allow their HR and $\dot{V}O_2$ to return to baseline and then to cycle at 35 RPM for as long as they are able, but for a maximum of eight minutes. The symptoms that patients were asked to report were fatigue and breathlessness.

5.2.3.3 Symptom-limited incremental exercise test

This consisted of 1 minute of exercise at 35 RPM unloaded, 1 minute at 10 watts.min^{-1}, then increasing by 5 watts.min^{-1} until the end of exercise. Sampling and data collection were for the symptom-limited, constant, unloaded exercise test.

5.2.3.4 ICU functional status score

The ICU-FSS was measured for all patients at each testing session. The ICU-FSS contains two functional tasks from the FIM and three additional tasks that are relevant and feasible to perform in the ICU setting. All five functional tasks are evaluated using the 7-point scoring system of the FIM, with higher scores indicating higher function [247]. The full description and scoring of the ICU-FSS is shown in *Appendix B.3*.

5.2.3.5 General practice physical activity questionnaire

The patient's pre-admission activity levels were estimated from their GPPAQ score (*Appendix B.4*). This information was taken from the patient and/or their relatives.

5.2.3.6 Borg rate of perceived exertion

Patients were asked to report their perceived exertion using the original Borg category scale (6 to 20 points) [174], at the beginning and end of the exercise sessions (*Appendix B.5*).

5.2.3.7 Ergometry validation

A Monark Cardio Rehab 831E ergometer (Monark, Vansbro, Sweden) was used for the arm cycle ergometry. The power output of cycle ergometers can vary considerably depending on the RPM at which they are used. I anticipated that patients would only be able to cycle at 40 RPM or lower. Monarch were requested to test both the lowest RPM at which a stable power output could be achieved and the accuracy of this power output, before the ergometer was shipped. This testing was carried out in June 2011. The ergometer was re-calibrated after shipping, before the feasibility study began. The testing details from Monarch are shown in *Appendix B.6.* Monarch advised that the lowest RPM at which a stable power output could be assured was 31 RPM. However, the device only provided a stable RPM output at 33 RPM. I therefore chose 35 RPM as the lowest RPM that was acceptable. At 35 RPM the lowest work output from the device was 4 watts (when the ergometer was programmed at 0 watts).

5.2.3.8 Polar heart rate monitor

A Polar RS800CX heart rate sensor (Polar, Kempele, Finland) was used to record continuous heart rate data. These data were used for heart rate variability analysis and HRrec.[1] The sensor attached to the anterior aspect of the patient's chest via an elasticated strap. The device recorded data at 60 Hz and was downloaded and viewed using Polar software (Polar Protrainer 5).

5.2.3.9 Patient experience of exercise questionnaire

A pre- and post-exercise questionnaire was designed to gather information to generate themes for a semi-structured interview to conduct with patients during follow-up. It was hoped that the questionnaire could compare the patients' experience of cycle ergometry with normal rehabilitation. The questionnaire is in *Appendix B.7.*

5.2.4 Results

5.2.4.1 Recruitment

Thirteen patients were recruited between December 2011 and July 2012. Data were collected on 12 patients. The Consort diagram is shown in *Figure 5.1.* Forty-one sessions were recorded; 21 rehabilitation, 11 cycling and 9 both.

5.2.4.2 Feasibility of arm ergometry

Ten of the 13 enrolled patients were able to participate in arm cycle ergometry. Six of the 10 patients were able to complete three minutes of arm cycling on or by their 3rd cycle test.

[1] HRrec, the rate of heart rate deceleration. See chapter 3.

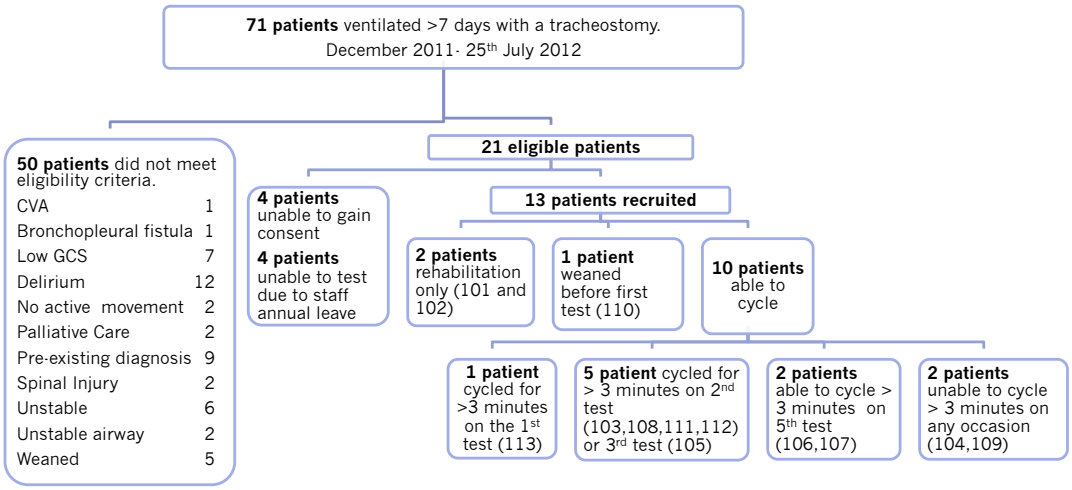


Figure 5.1: Pilot Consort diagram.

Four of the patients achieved 35 RPM. Two patients completed three minutes of cycling on subsequent cycle tests. Therefore, four of the ten patients met the randomisation criteria for the incremental protocol. Two patients (0105 and 0108) were randomised to the constant load group, the third patient (111) weaned before the incremental test session and the fourth declined to participate in further tests.

5.2.4.3 Breathlessness measured by the Borg breathlessness scale

Three of the ten patients were able to report their breathlessness on the Borg scale on one or more occasions. The remaining patients were either unable to comprehend the scale or were too fatigued to comply with the process after the rehabilitation session.

5.2.4.4 Patient experience of exercise questionnaire

Five questionnaires out of 41 were completed. Again, most patients were either too fatigued at the end of a session or did not appear to understand the questions.

5.2.4.5 Timing and duration of enrolment

While it was possible to test patients three times per week, low staffing levels often prevented completing the cycling session on the days stated within the protocol. Additionally, only being able to follow the patients for three weeks also limited the amount of data that was collected.

5.2.4.6 Heart rate

Placing the polar heart rate monitor on patients was challenging. In some patients it was necessary to roll the patient to get the monitor in place, which in itself would have a metabolic cost. Continuous heart rate data were obtained for 12 of 41 tests in seven of the 12 patients. In one patient (3 tests) there were no data as the Polar strap was too small. One patient (4 tests) declined to have the Polar strap placed. In three patients (6 tests) no data were obtained due to excessive noise in the recording. The remaining absent data (28 tests) were spread over the other seven patients and were again due to excessive noise within the data.

5.2.4.7 Heart rate variability

There was too much noise within the polar data to be able to isolate the clear five minute segments required to compare at rest, during exercise and then during recovery data, in any of the recordings.

5.2.4.8 Lactate

Only one patient, from whom I gained consent for blood sampling, had arterial access on the test days.

5.2.4.9 Intra patient repeatability of values

Generating data to test the repeatability of values was challenging. Patients were too fatigued following one single cycle or rehabilitation session to be able to repeat the same challenge.

5.2.5 Discussion

The feasibility study highlighted a number of factors that required addressing. Despite a 61% recruitment rate of eligible patients, far fewer patients were enrolled than anticipated. Only 21 (29%) of the 71 patients ventilated via a tracheostomy in the 7 month period were eligible for recruitment, with nearly a quarter excluded due to delirium which precluded rehabilitation. It was anticipated that two thirds of the patients would be able to cycle for $\geq$3 minutes and be randomised into the constant load or incremental groups. However, only 4 of 13 patients (30%) were randomisable. Therefore, a further 66 patients would need to be recruited (roughly a further three years of data collection) to gain ten patients per group. However, if only 30% of the rehabilitation population were able to meet the criteria for an incremental test, then any model or test created would not be generalisable to the current ICU population at UCH. I therefore conclude from the results of this pilot investigation that an incremental ergometry test was not feasible and eliminated incremental tests as a method of establishing exercise

intensity in mechanically ventilated patients.

The low consent rate for blood sampling during exercise raised two challenges. The first was that this led to lack of my exposure to the process of obtaining blood samples mid-exercise while also running the MGU, recording stages of the tests and supervising the exercise session. This lack of practice resulted either in samples not being taken in a timely manner, or in written data not being recorded precisely. The latter, more ethical issue, was that few samples would be obtained so that no useful comparisons could be made. Therefore, with only one person performing data collection, regular lactate measurements were infeasible due to the complexity of the data collection process.

Surprisingly few patients reported their breathlessness using the Borg scale both before and after exercise. This may have in part been due to the original 6-20 scale that was being used. A majority of patients did not want to rate their breathlessness as they were too fatigued at the end of the session. I therefore changed to the modified Borg scale, with the expectation that it would increase the number of patients able to report their breathlessness.

Similarly, no useful data were being obtained from the questionnaire. Few patients felt able to complete a questionnaire after exercise. This process was also abandoned.

There were several challenges associated with the Polar heart-rate monitor. The first was that it was not possible to record HRV data from the Polar monitor. Despite the monitor being used widely and with an extensive literature base, I was unable to isolate the two 5 minute segments, one during rest and one during recovery, required for comparison in any of the 12 recording sessions. Secondly, having the HR monitor placed to record resting, exercise and recovery HR was a considerable effort for the patient, even before the exercise session had started. Although abandoning the Polar monitor meant that I would be unable to calculate HRrec in future patients, I decided to record resting and peak exercise HR from the patient's ECG monitor and to investigate the feasibility of downloading continuous data from the ECG monitor.

5.3 Modification of protocol

I decided that more information would be obtained by concentrating on gaining constant load data. Therefore I submitted a major amendment to the ethics committee to change the protocol.

5.3.1 Outcomes

Primary outcomes.

i) Whether or not the patient was able to complete 3 minutes of constant load exercise at any time point.

ii) Whether or not it was possible to estimate the patient's anaerobic threshold from constant load data [246].

iii) Whether or not it was possible to calculate the patient's mean response time from constant load data.

Secondary outcomes. To assess the following during every constant load and rehabilitation session:

i) peak $\dot{V}O_2$ ($mL.Kg.^{-1}min^{-1}$),

ii) excess post-exercise oxygen consumption (mL),

iii) rate of perceived exertion using the Borg 0-10 (ordinal) scale.

I aimed to calculate:

iv) the mean response time of the $\dot{V}O_2$ uptake kinetics, from any constant load test that achieved a steady state,

v) the mean $\dot{V}O_2$ ($mL.Kg.^{-1}min^{-1}$) and total VO_2 ($mL.Kg.^{-1}$) for each level of rehabilitation achieved at each session,

vi) the sensitivity to change over time of; the patient's mean response time from constant load data, peak $\dot{V}O_2$ ($mL.Kg.^{-1}min^{-1}$), excess post-exercise oxygen consumption (mL), rate of perceived exertion using the Borg 0-10 (ordinal) scale, and for each level of rehabilitation achieved at each session, total VO2 (mL.Kg.-1).

5.3.2 Materials and methods

I amended the protocol to observe patients on three occasions per week until they were liberated from mechanical ventilation. No arterial blood gases were to be taken mid-exercise. If consent was gained from patients with arterial access then samples would be taken at the beginning and end of the exercise sessions. HRrest and HRpeak during exercise would be recorded from the patient's bedside monitor. Patients would be asked to rate their perceived exertion using the modified Borg scale.

5.3.3 Analysis

5.3.3.1 MedGraphics Ultima data averaging

The previously validated MGU device was used to measure oxygen consumption via a flow-sensor. When patients are at rest the MGU displays $\dot{V}O_2$ data with relatively little noise. However, exercise increases V_T, $\dot{V}_E$ and flow entropy. This increase in entropy is associated with an escalation in the noise of the recorded data as seen in *Figure 5.3*. Fluctuations in V_T and in delivered F_iO_2 are in part responsible for the noise. The MedGraphics software *Breeze Suite* allows basic filtering of low V_T, $\dot{V}O_2$ and $\dot{V}O_2$ data and low and high RQ. The majority of the fluctuations in F_iO_2 can be filtered out using the RQ filter *(Figure 5.3 (filtered))*, as a low F_iO_2 results in an unphysiologically elevated RQ. Removing the low V_T values further reduces the noise of the recorded data. The *Breeze Suite* software allows further smoothing of the data by creating a moving average. Moving or rolling averages are used to reduce the amount of noise within recorded data. The *Breeze Suite* inbuilt averaging methods are the middle 5 of 7 breaths, median of 7 breaths or mean of 8 breaths. However, it was unclear if removing the low but not the high values through the in-built filtering method, increased the minimum, maximum and/or mean values.

Objective. To establish if the inbuilt software analysis elevated mean, minimum and maximum values as a result of filtering only low $\dot{V}O_2$ $\dot{V}CO_2$ and V_T values.

Methods. I wrote a PASW 21 (IBM) script (*Appendix B.8*) to filter and average the raw data of ten rehabilitation sessions of patients recruited in the pilot study. The same time segment of each test was used for analysis in both PASW 21 and *Breeze Suite*. An example of the raw plots of each parameter $\dot{V}O_2$, F_iO_2, V_T, RQ, and the final $\dot{V}O_2$ plot are shown in *Appendix B.9*.

Analysis. Comparisons were made between the mean, minimum and maximum $\dot{V}O_2$ values obtained from the PASW 21 and *Breeze Suite* smoothing. Bland Altman plots were created *(Figure 5.2)* and the bias and precision calculated *(Table 5.2)*.

Results. The *Breeze Suite* averaging and filtering gave mean values that were minimally higher than the PASW 21 values, minimum values that were lower and maximum values that were higher. In terms of establishing values for area under the curve (total VO_2 during a rehabilitation session) the mean value would be the most important, followed by the maximum value. Therefore, using the middle 5 of 7, mean values had a 0.72% positive bias with narrow 95% LOA (7.02% to 8.47%). Minimum values would have a -6.5% bias, and 95% limits of

agreement (LOA) of -18.67% to 5.56%. Maximum values would have a 8.3% positive bias with 95% LOA of -4.11% to 20.7%.

Conclusion. The middle 5 of 7 breath technique was chosen over the other averaging techniques as it provided the values with the least bias and the narrowest 95% confidence interval for the difference between PASW 21 and *Breeze Suite* values.

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	Mean values (%)			Min values (%)			Max values (%)		
	Mid 5 of 7	8BM	Median of 7	Mid 5 of 7	8BM	Median of 7	Mid 5 of 7	8BM	Median of 7
Bias	0.72	2.19	0.28	-6.55	-3.85	-7.2	8.3	7.77	11.92
Upper 95% LOA	7.02	-7.96	-6.14	-18.67	-13.19	-19.12	-4.11	-5.95	1.26
Lower 95% LOA	8.47	12.34	6.71	5.56	5.5	4.72	20.7	21.5	22.59

8BM = 8 breath mean, LOA = limits of agreement.

Table 5.2: Level of agreement as a percentage for the three averaging methods.

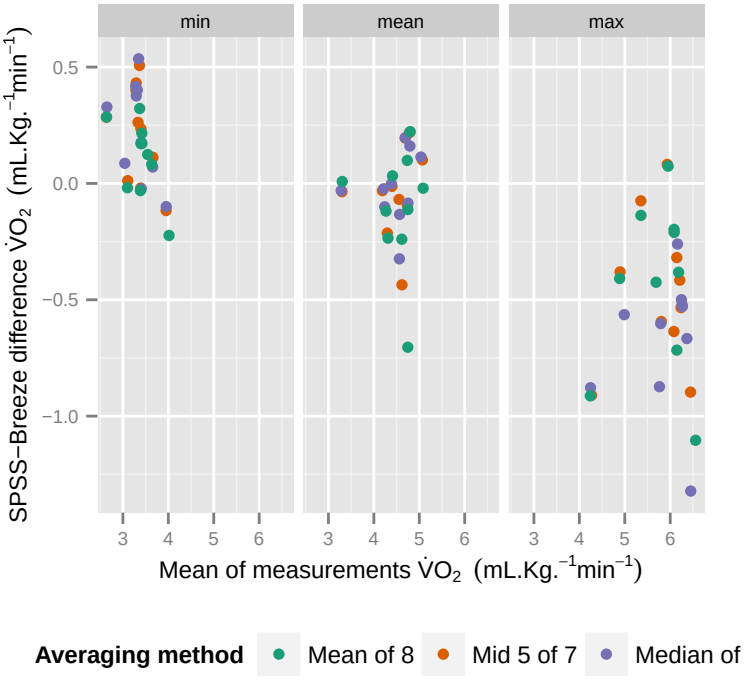


Figure 5.2: Bland Altmam plots of three potential averaging methods in *Breeze Suite*. Filtered $\dot{V}O_2 \geq 175$, VT$\geq$240, RQ = 0.9-1.2

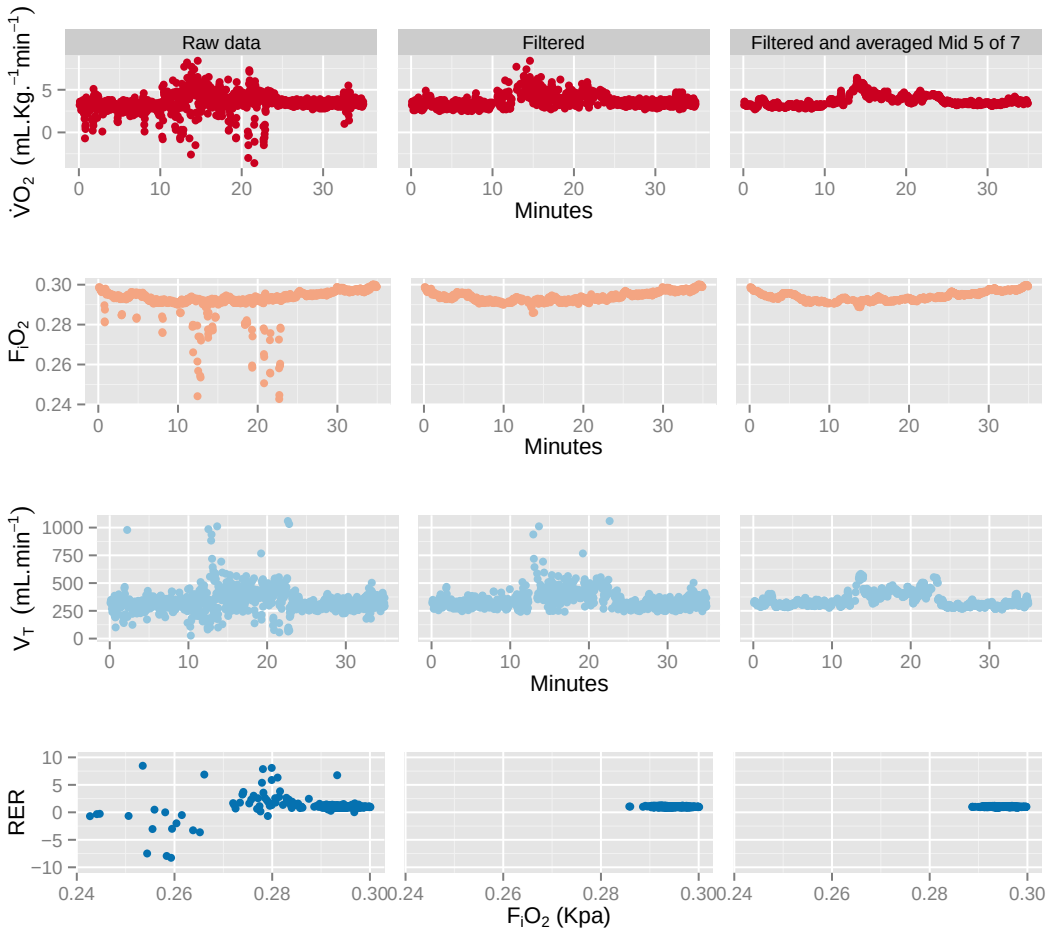


Figure 5.3: *Breeze Suite* filtering and averaging graphs.

5.3.3.2 Arm cycle ergometry data

The cycle tests were categorised as to whether or not the patient managed ≥3 minutes of ergometry or not. Factors that might influence a patient's ability to cycle ≥3 minutes were explored using a multilevel, univariate, generalised linear mixed effects model [11, 248]. The binary outcome was the ability to cycle for 3 minutes or not on one or more occasions. A maximum of two tests were entered per patient. The tests were chosen as follows:

i) if the patient only completed 1 cycle test, this was used,

ii) if the patient either managed to cycle for ≥3 minutes on every occasion or if they were unable to cycle ≥3 minutes on any occasion, then the first and last tests were used, or

iii) if the patient was unable to cycle on their first attempt but was able to do so on subsequent attempts, then the patient's first test and the first test where they managed ≥3 minutes were used.

Explanatory factors and variables were; i) age, ii) gender, iii) weight, iv) the patient's pre-admission GPPAQ score[2], v) the patient's highest SOFA score [249], vi) the duration of mechanical ventilation at recruitment. vii) ICU-FSS[3] viii) SOFA on the day of test, ix) lactate, x) Hb, xi) HRrest, xii) HRrest / calculated HRmax (cHRmax)[4], xiii) HRpeak / cHRmax. As only one factor was found to be statistically significant, no multivariate regression was performed. Analysis of the residuals was performed to identify outliers, by calculating DFBETA's[5] and Cook's distance[6] [250].

Estimation of anaerobic threshold. An inability to reach steady-state (identified as a plateau in $\dot{V}O_2$) during a constant load ergometery test is reported to be indicative of a workload above the subject's anaerobic threshold [242, 251]. Therefore, unless a subject has abnormally low $\dot{V}O_2$ uptake kinetics, a plateau in $\dot{V}O_2$ should be established by three minutes during a constant load exercise-test, provided the workload is below the subject's AT. In patients who did not reach a plateau (making the assumption that $\dot{V}O_2$ uptake kinetics were not so abnormal to have not reached steady state within the duration of the test), it is possible to estimate their anaerobic threshold. Arm cycle ergometry is considered to consume

[2]GPPAQ. General practice physical activity questionnaire, see *Appendix B.4*

[3]ICU-FSS, ICU functional status score, see *Appendix B.3*.

[4]cHRmax = 220-age

[5]DFBETA's are a measure that standardises the absolute difference in parameter estimates between a (mixed effects) regression model based on a full set of data, and a model from which a (potentially influential) subset of data is removed. DFBETA refers to how much a parameter estimate changes if the observation in question is dropped from the data set.

[6]Cook's distance refers to how far, on average, predicted values move if the observation in question is dropped from the data set.

oxygen as follows [252];

$$\dot{V}O_2\ (mL.kg.^{-1}min^{-1}) = 3 * \frac{\text{work rate}}{\text{body mass}} + resting\ \dot{V}O_2\ (mL.kg.^{-1}min^{-1}) \tag{5.1}$$

$$\text{where work rate is in } kg.m.^{-1}min^{-1}, \text{ or } 1\ watt = 6.12\ kgm.min^{-1}$$

Mean response time. Calculation of the mean response time of $\dot{V}O_2$ assumes it is possible to model the $\dot{V}O_2$ response during phase I and II of exercise, to a mono-exponential curve. Tau (the time constant), i.e. the time taken for $\dot{V}O_2$ to increase by a proportion of 0.63, can then be estimated. None of the six tests that reached a plateau fitted a mono-exponential curve. Therefore this calculation would not give a justifiable estimation of tau. Although it should be possible to estimate tau from individual graphs, the quality of the data is such that I could not accurately determine the plateau value.

Excess post-exercise oxygen consumption. Given that the uptake kinetics of those who reached a plateau in their $\dot{V}O_2$ are not mono-exponential, is is not justifiable to equate the O_2 deficit and the O_2 debt. As patients who did not reach a plateau were also most likely to be over their AT, this also suggests that O_2 deficit and O_2 debt would not equate.

5.3.3.3 Analysis of rehabilitation data

The total session VO_2 (mL.Kg^{-1}) was estimated by calculating the area under the individual $\dot{V}O_2$ (mL.Kg.$^{-1}$min^{-1}) curves bound by the start of the rehabilitation session (defined as the time the patient initially began to SOEB) and the time $\dot{V}O_2$ returned to within 10% of the value at rest *(Figure: 5.4)*.

$$\text{total session } VO_2\ (mL.kg.^{-1}) = \tag{5.2}$$

$$\text{duration of the session (minutes) * mean } \dot{V}O_2\ (mL.Kg.^{-1}min^{-1}) \text{ of the session}$$

The VO_2 (mL.Kg^{-1}) attributable to the rehabilitation session itself, i.e. the VO_2 (mL.Kg^{-1}) consumed above that consumed at rest, was calculated by subtracting the equivalent VO_2 (mL.Kg^{-1}) at rest from the total session VO_2 (mL.Kg^{-1}) *(Figure 5.4)*. $\dot{V}O_2$ (mL.Kg.$^{-1}$min^{-1}) at rest was calculated as the mean $\dot{V}O_2$ (mL.Kg.$^{-1}$min^{-1}) during 10 minutes where there was a <10 % change in $\dot{V}O_2$ at rest prior to the rehabilitation session. The VO_2 values attributable to the rehabilitation are presented as a percentage of the resting VO_2.

$$\%\text{ change in } VO_2 = \frac{\text{Total session } VO_2\ -\ \text{Rest } VO_2}{\text{Rest } VO_2} * 100 \tag{5.3}$$

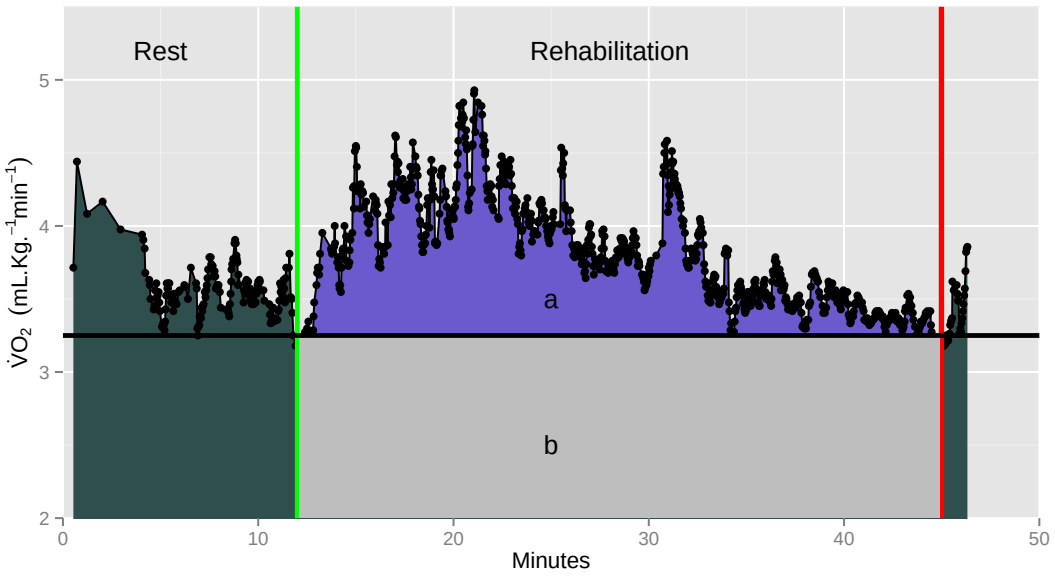


Figure 5.4: Oxygen consumption calculation for rehabilitation sessions. a = VO_2 attributable to exercise session, b = Total VO_2 at rest, a + b = Total session VO_2.

In order to make comparisons between the percentage change in VO_2 between different rehabilitation activities, the rehabilitation activities needed to be categorised. This was done by categorising as they would be in clinical practice; i) sit over the edge of the bed, ii) sit over the edge of the bed and balance exercises, iii) sit to stand, iv) sit to stand >1, v) bed chair transfer. To increase the robustness of the analysis, the 5 categories were then collapsed down into 3 and then 2 groups. (*Table 5.8*). Multilevel univariate regression was carried out with the data grouped by patient and the percentage change in VO_2 as the dependent variable.

Further multilevel univariate regression was carried out to explore other potential explanatory factors or variables for the percentage change in total session VO_2 (or mean session $\dot{V}O_2$). I again grouped the data by patient, with the dependent factor as percentage change in session VO_2 and the explanatory variables and factors as; i) test number, ii) test day, iii) rehabilitation activity (sitting or standing), iv) number of prior rehabilitation sessions, v) ICU-FSS on the day of testing, vi) time to first rehabilitation session, vii) current pressure support, viii) exercise pressure support, ix) F_iO_2, x) the increase in pressure support from resting level, xi) CRP, xii) Hb, xiii) temperature, xiv) WCC, xv) SOFA, xvi) HRrest, xvii) HRmax, xviii) HR change, xix) weight, xx) gender, xxi) age, xxii) height, xxiii) GPPAQ, xxiv) HRrest/ cHRmax, xxv) HRpeak / cHRmax.

The factors reaching the 95% statistical significance level were added to a multilevel multivariate linear mixed effects model. Interaction terms were compared using ANOVA of the

log-likelihoods of the relevant models. AIC[7] and BIC[8] values were used to select the best model fit. The residuals of the final model were then plotted and examined for influential cases.

5.3.4 Results

5.3.4.1 Recruitment

A further 31 patients were recruited between August 2012 and March 2015, giving 44 patients and 127 tests in total. No data were collected for two patients, as one weaned from mechanical ventilation on the morning of the first test and the other became cardiovascularly unstable on the morning of the first test and remained so beyond the study duration. See *Figure 5.5* for the consort diagram of the analysis. There were two periods of non-recruitment: February 2013 - November 2013 (maternity leave), and July 2014 - September 2014 (equipment failure).

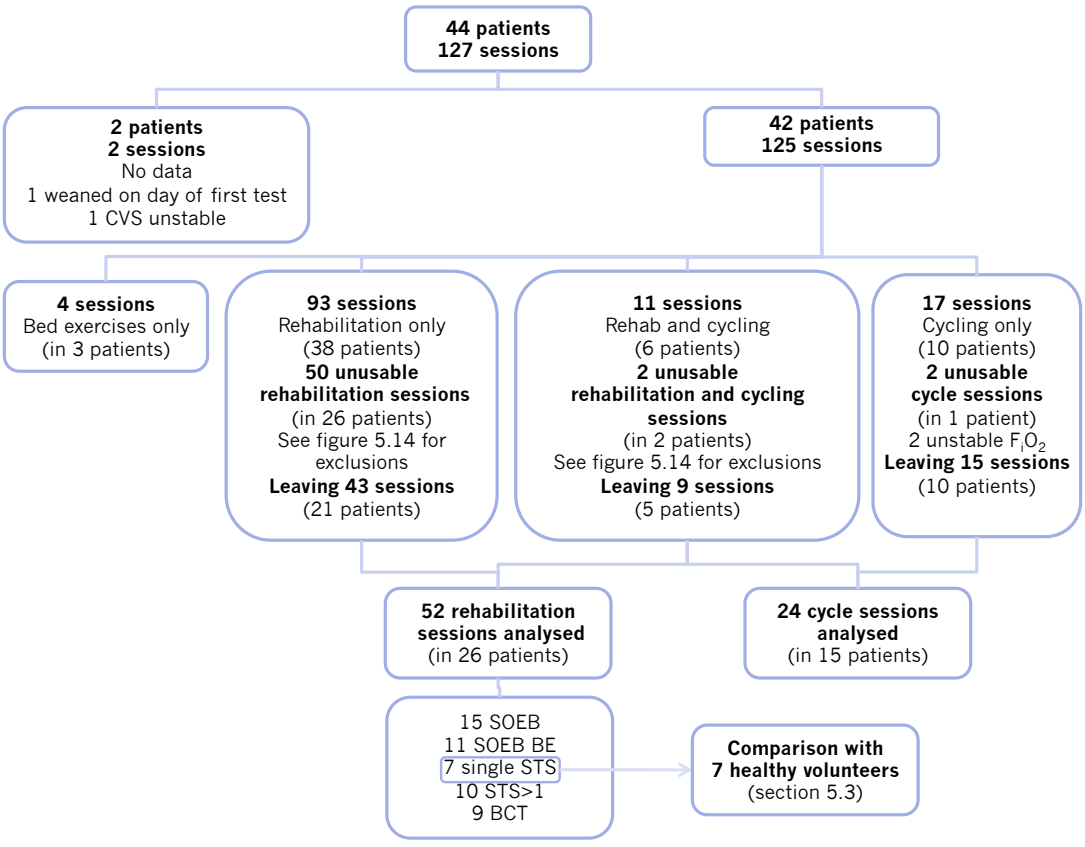


Figure 5.5: Consort diagram of rehabilitation and cycle data analysis. SOEB = sit over edge of bed, BE = balance exercises, STS = sit to stand, BCT = bed chair transfer.

[7]AIC: Akaike's information criterion.

[8]BIC: Bayesian information criterion.

5.3.4.2 Cycle ergometry

Fifteen patients (7 male and 8 female) cycled in total (*Table 5.3*), giving 24 cycle tests, 12 of which lasted ≥3 minutes. Eleven of the 12 tests where patients achieved ≥3 minutes of arm ergometry are plotted in *Figure 5.8*. There were no $\dot{V}O_2$ data for one patient (103) who weaned from mechanical ventilation on the morning of the first cycle test. A total of 10 patients were able to cycle for ≥3 minutes on one or more occasions.

Characteristics of patients able to cycle ≥3 minutes The only variable significantly associated with an ability to cycle ≥3 minutes was the patient's physical function level (ICU-FSS) on the day of testing (*Table 5.4*). Of note, there is no variance in the random (patient grouping) part of the model, showing that it was not necessary to use a multilevel model in this instance. The DFBETA's and Cook's distance indicated that none of the patients were overly influencing the model (*Figure 5.7*). The odds of being able to cycle for ≥3 minutes increased by 14% (95% CI: 0.003 to 27%) for every point increase in ICU-FSS (p = 0.05) (*Figure 5.6*).

Variable	n	Median	Min	Max
Age (years)	15	70	50	80
weight (Kg)	15	70	40	119
MV prior to recruitment	15	23	16	61
Highest SOFA	15	8	2	13
GPPAQ	15	2	1	4

MV = mechanical ventilation

GPPAQ = General practice physical assessment questionnaire

Table 5.3: Cycle patient characteristics.

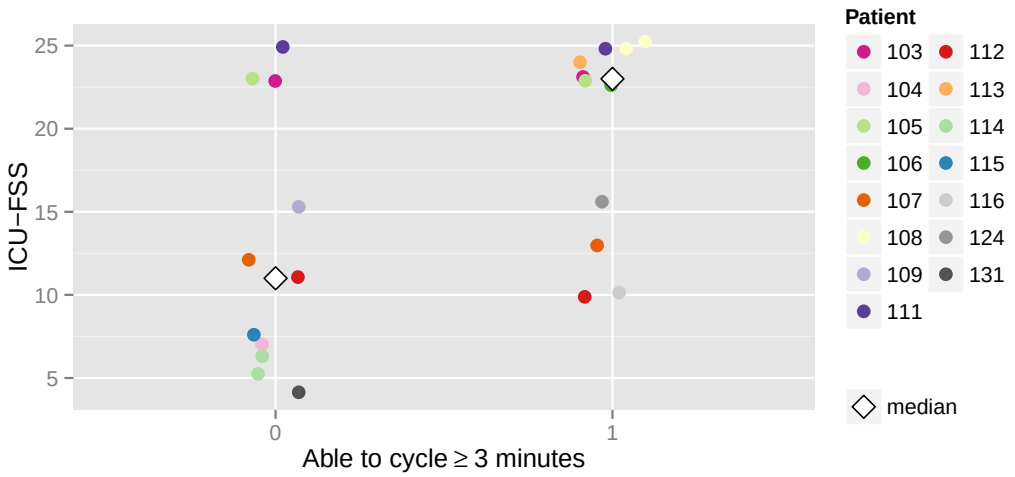


Figure 5.6: ICU-FSS and ability to cycle ≥3 minutes.

	M18
Intercept	−2.25
	(1.20)
ICU-FSS	0.14*
	(0.07)
AIC	31.41
BIC	34.68
Log Likelihood	−12.71
Num. obs.	22
Num. groups: pid	15
Variance: pid.(Intercept)	0.00
Variance: Residual	1.00

*$p < 0.05$. M18 = ICU-FSS as the fixed effect.

Table 5.4: Multilevel logistic regression estimate for ability to cycle ≥3 minutes.

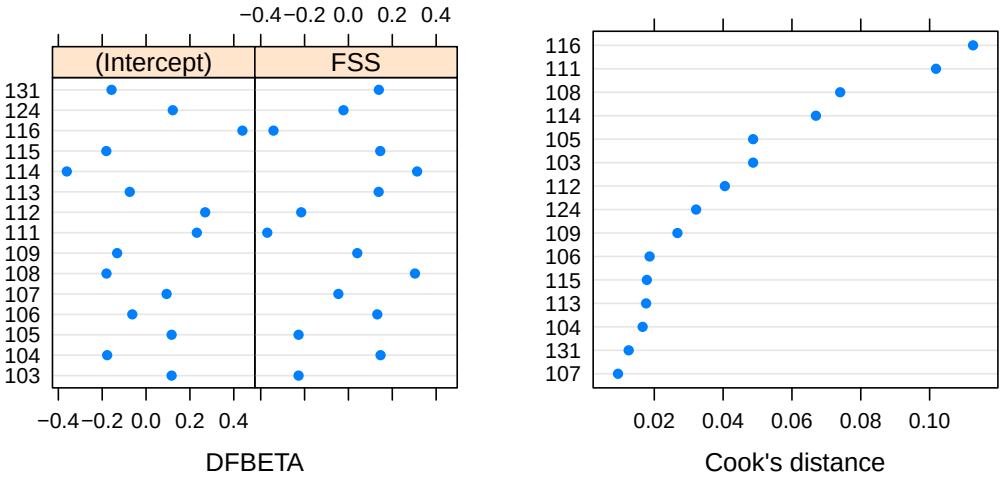


Figure 5.7: DFBETA's and Cook's distance for ICU-FSS model (M18) of ability to cycle ≥3 minutes. DFBETA's standardise the absolute difference in parameter estimates between a (mixed effects) regression model based on a full set of data, and a model from which a (potentially influential) subset of data is removed. DFBETA refers to how much a parameter estimate changes if the observation in question is dropped from the data set. Cook's distance refers to how far, on average, predicted values move if the observation in question is dropped from the data set.

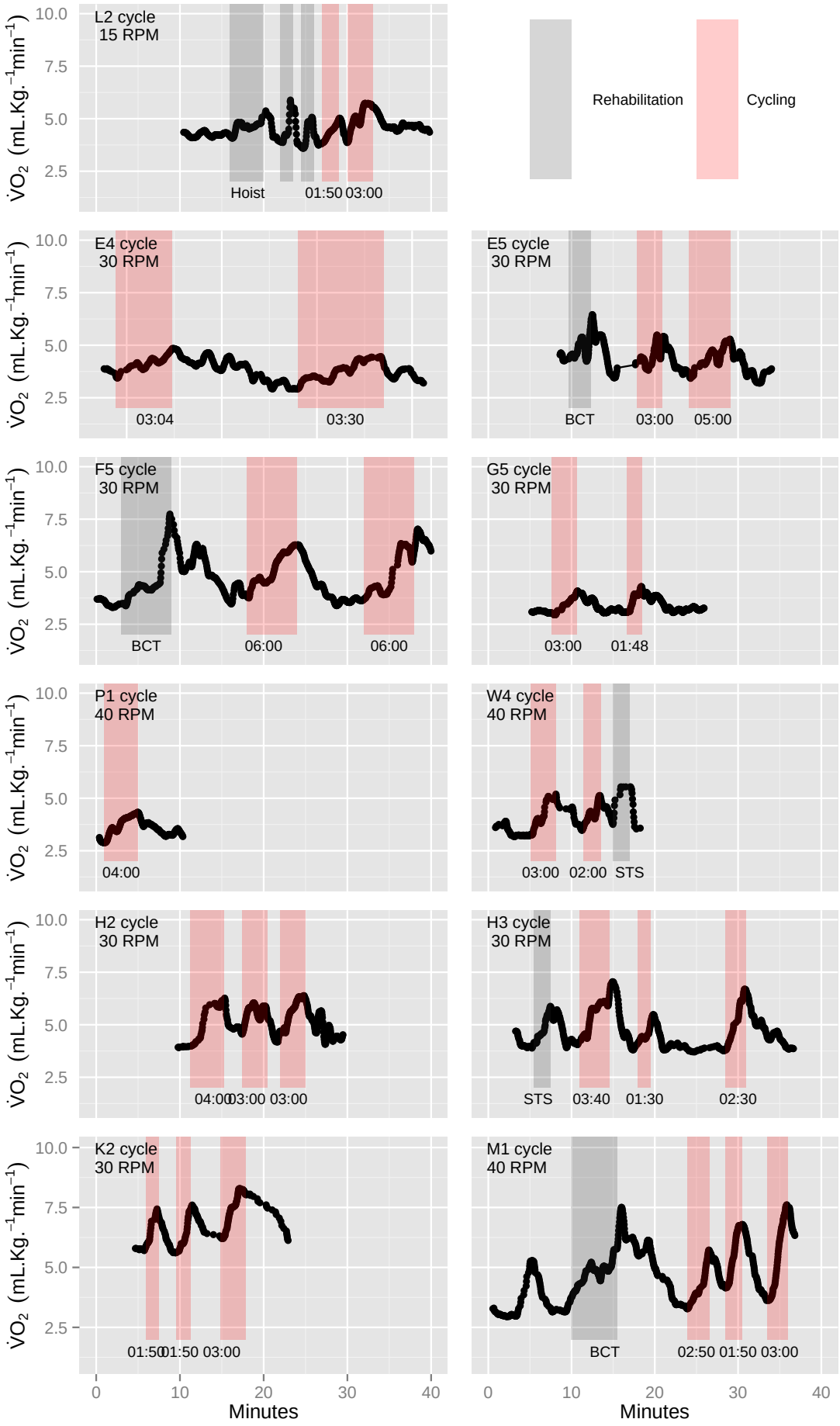


Figure 5.8: $\dot{V}O_2$ plots for individual cycle tests where ≥3 minutes ergometry was achieved during an exercise session. STS = sit to stand, BCT = bed chair transfer.

Estimation of anaerobic threshold. Reviewing the plots of the patients who cycled for ≥3 minutes (*Figure 5.8*), six patients did not reach a plateau in their $\dot{V}O_2$ (E4/E5,F5,G5,K2,M1,P1) and while three did (H2/H3,L2,W4). If the assumption is made in the case of patients who did not reach a plateau, that their $\dot{V}O_2$ uptake kinetics were not so abnormal as to have not reached steady state within the duration of the test, then the estimation for AT in the six patients who cycled for ≥3 minutes but who did not reach steady state by the end of their cycle duration are given in *Table 5.5*.

Patient	Anaerobic threshold (mL.Kg.min)			Duration	
	7 watts	10 watts	15 watts	(Min)	RPM
105	4.81	6.22	7.64	5:00	30
106	4.71	6.02	7.33	6:00	30
107	4.09	5.19	6.28	3:00	30
111	7.54	9.58	11.62	3:00	30
113	5.48	7.21	8.95	3:00	40
116	4.16	5.42	6.67	4:00	40

Table 5.5: Estimated anaerobic thresholds, with the assumption that patients should have reached a plateau in $\dot{V}O_2$ within the duration of the test.

5.3.4.3 Normal rehabilitation sessions

A total of 104 rehabilitation sessions were assessed in 38 patients. Two patients were not assessable (see earlier). Patients were ventilated a median of 22.5 (range 4-175) days before their first rehabilitation session and a median of 30 (range 11-175) days before their first measured exercise session. It was possible to calculate the percentage change in $\dot{V}O_2$ from rest in 52 of the 104 tests. Of these, there were 15 SOEB episodes, 11 SOEB and balance work, 7 single STS and 10 STS ≥1 and 9 bed chair transfers (*Table 5.7*). The reasons why some of the data were unusable are shown in *Table 5.13*. The minimum rehabilitation session duration was 5:35 minutes to transfer from bed to chair. The maximum duration was 39:21 to SOEB and to stand one or more times.

Box plots of the rehabilitation categories and i) the mean $\dot{V}O_2$ ($mL.Kg.^{-1}min^{-1}$) of the session, ii) the total VO_2 of the session ($mL.Kg^{-1}$), iii) the percentage change in VO_2 of the session, are shown in shown *Figure 5.9*. Discrimination between rehabilitation activities was only possible when the rehabilitation activities were categorised into sitting or standing *(Table 5.9)*. The mean percentage increase in VO_2 from rest to SOEB ± balance exercises was 23.25% (SD 11.16%) and the mean percentage increase from rest to standing and or transferring from

bed to chair was 34.8% (SD 13.34%).

The only factors that demonstrated a statistically significant univariate association with the percentage change in the total session VO_2 (or mean session $\dot{V}O_2$), were rehabilitation activity, ICU FSS, the number of prior rehabilitation sessions the patient had received, and the pressure support increment (*Table 5.10*). ICU-FSS was highly correlated with the rehabilitation activity, presumably because the patient's physical function (measured by ICU-FSS) improvement, meant they were more likely to engage in a higher level of activity (*Figure 5.10*). When activity and ICU-FSS were added individually (M28) to the analysis and then compared to a model with the interaction term ICU-FSS:Rehabilitation activity (M27) *(Table 5.11)*, analysis of the variance of the log-likelihoods of M27 and M28 demonstrated that the interaction was statistically insignificant ($p = 0.31$). The removal of prior rehabilitation sessions from activity, ICU-FSS and pressure support increment (M29 vs. M30) *(Table 5.11)*, did not significantly change the model fit ($p = 0.79$). When the residuals of M30 were plotted *(Figure 5.11)*, patient 137 was identified as a significant outlier. The factors that most influenced the percentage change in $\dot{V}O_2$ (and VO_2) were ICU-FSS, the pressure support increment and the rehabilitation activity. Therefore a patient who could SOEB with an ICU-FSS of 0 and a pressure support increment of 0 would expect an 11.88% (95% CI: 4.45 - 19.31%) increase in their $\dot{V}O_2$. A patient standing with an ICU-FSS of 0 and no increase in their pressure support would expect a 1.53% (95% CI: -10.95 to 7.89%) decrease in their $\dot{V}O_2$. It is worth noting this is a very unlikely event i.e standing a patient with no muscle activity, as the lowest ICU-FSS that patients stood with was 10. For every point increase in ICU-FSS a 1.21 % (95%CI: 0.50; 1.93%) increase in $\dot{V}O_2$ could be expected. For each cm H_2O increase in pressure support, a further 1.41% (95% CI: 0.79-2.03%) increase in $\dot{V}O_2$ could be expected.

The calculated pseudo R^2 for this model is 0.63. This suggests that the activity, patients' functional status and pressure support increment explain up to 63% of the change seen in $\dot{V}O_2$ during rehabilitation sessions in the ICU. The remainder of the explanation is elusive.

Variable	n	Median	Min	Max
Age (years)	38	69	31	86
weight (Kg)	38	70	35	119
MV prior to recruitment	38	28	11	175
Highest SOFA	38	10	2	14
GPPAQ	38	2	1	4

MV = mechanical ventilation

GPPAQ = General practice physical assessment questionnaire

Table 5.6: Rehabilitation patient characteristics.

Rehabilitation	n	Session Duration			Rehabilitation Duration			Recovery Proportion		
Activity		Min	Median	Max	Min	Median	Max	Min	Median	Max
SOEB	15	06:11	15:00	36:36	04:34	08:46	23:28	0.20	0.51	0.69
SOEB & balance	11	13:19	21:04	31:45	06:51	13:38	17:38	0.18	0.34	0.59
STS x1	7	10:55	18:32	26:19	05:06	10:17	16:11	0.29	0.37	0.72
STS > 1	10	07:44	22:04	39:21	05:53	15:13	25:10	0.22	0.31	0.47
MOS or BCT	9	05:35	12:07	28:04	02:52	07:43	28:04	0.00	0.35	0.49

SOEB = sit over the edge of bed, STS = sit to stand, MOS = march on spot, BCT = bed chair transfer.

Table 5.7: Rehabilitation session characteristics.

Categories	Rehabilitation activity				
5 categories	SOEB	SOEB with BE	STS x1	STS>1	BCT
3 categories	SOEB and SOEB with BE		STS x1	STS>1 and BCT	
2 categories	SOEB and SOEB with BE		STS x1 and STS>1 and BCT		

SOEB = sit over edge of bed, STS = sit to stand, BE = Balance exercises, BCT = bed chair transfer.

Table 5.8: Rehabilitation activity classification codes. Grouping rehabilitation activities to give five, three or two categories.

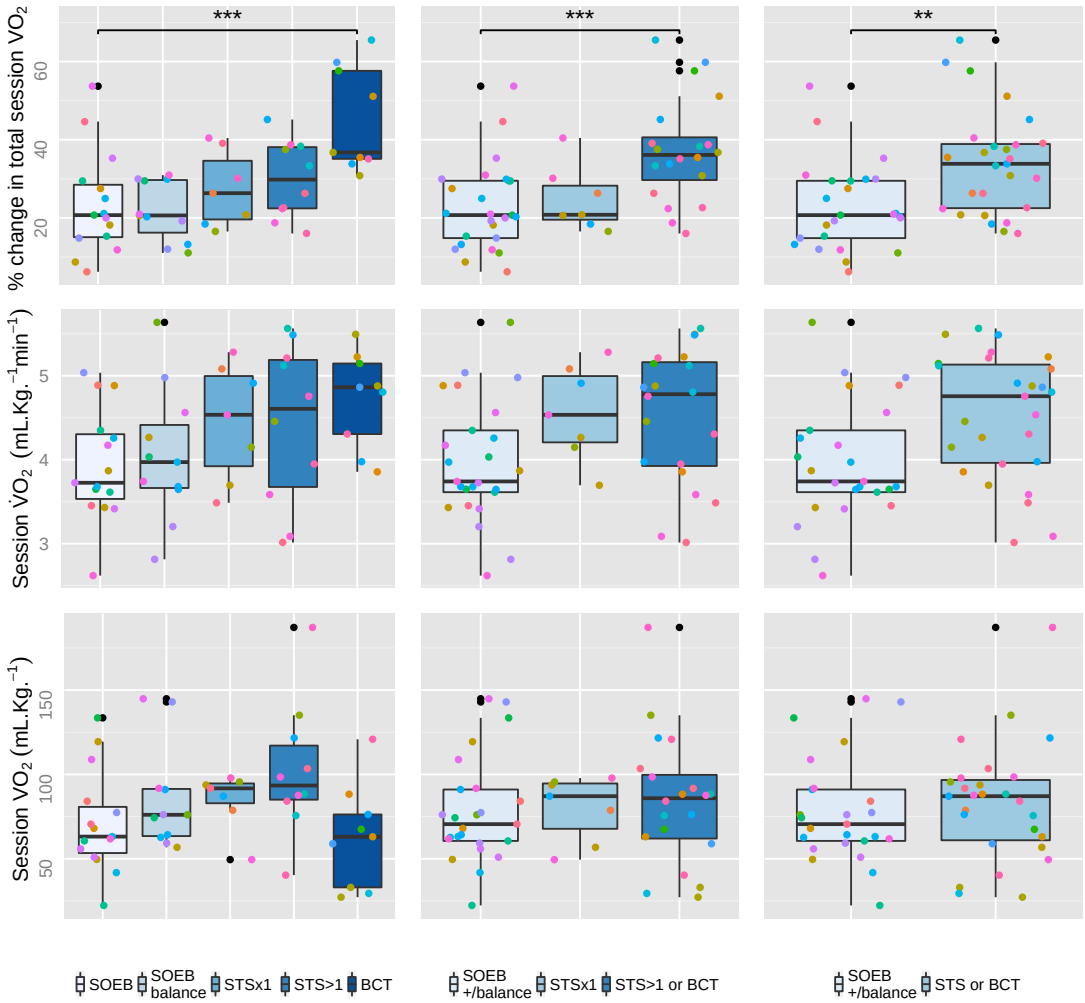


Figure 5.9: Box plots of session $\dot{V}O_2$ (mL.Kg.$^{-1}$min^{-1}), VO_2 (mL.Kg.$^{-1}$) and percentage change in session VO_2, with rehabilitation activity with 5, 3 and 2 categories.
***p <0.001, p ** <0.01, *p <0.05.

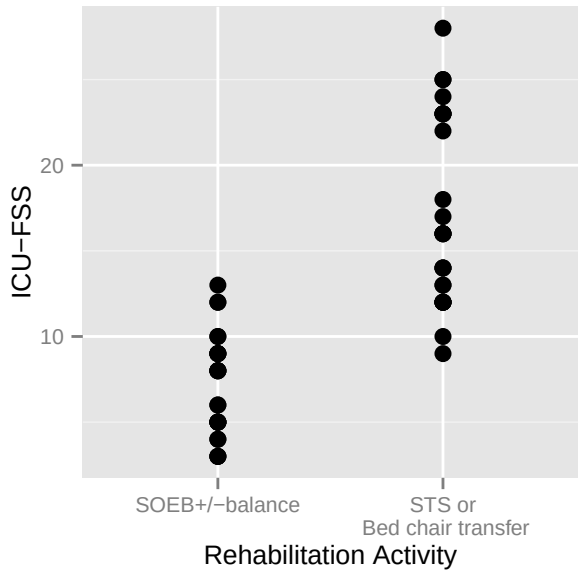


Figure 5.10: Rehabilitation activity and ICU-FSS interaction.

	5 categories	3 categories	2 categories
Intercept	23.53***	22.85***	23.25***
	(2.95)	(2.40)	(2.63)
SOEB with balance exercises (5 category)	−1.65		
	(4.37)		
STSx1 (5 category)	4.02		
	(5.03)		
STS>2 (5 category)	6.76		
	(4.57)		
BCT (5 category)	22.00***		
	(4.74)		
SOEB or SOEB with balance exercises (3 category)		2.40	
		(5.03)	
STS>2 or BCT (3 category)		14.52***	
		(3.56)	
STS or BCT (2 category)			11.56**
			(3.45)
AIC	406.78	411.08	414.25
BIC	420.44	420.84	422.06
Log Likelihood	−196.39	−200.54	−203.13
Num. obs.	52	52	52
Num. groups	26	26	26

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$. SOEB = sit over edge of bed, STS = sit to stand, BCT = bed chair transfer.

Table 5.9: Univariate linear regression estimates and and standard error of the means (SEM) for percentage change in VO_2 and the method of classifying the rehabilitation activity. SOEB is the reference category for the 5 category model. SOEB and SOEB with balance exercises represents the reference category for the 2 and 3 category models.

	Rehabilitation activity	ICU-FSS	Prehab	PSinc
Intercept	23.25***	14.74***	25.84***	26.73***
	(2.63)	(3.52)	(2.95)	(2.57)
STS or BCT	11.56**			
	(3.45)			
ICU-FSS		1.14***		
		(0.25)		
Prior rehabilitation			1.28*	
			(0.57)	
PS increment				1.67*
				(0.73)
AIC	414.25	406.21	416.35	415.35
BIC	422.06	414.02	424.00	423.00
Log Likelihood	−203.13	−199.11	−204.18	−203.68
Num. obs.	52	52	52	52
Num. groups	26	26	26	26

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$. SOEB = sit over edge of bed, STS = sit to stand, BCT = bed chair transfer.

Table 5.10: Univariate linear regression estimates for percentage change in VO_2. The reference category for rehabilitation activity is SOEB or SOEB with balance exercise.

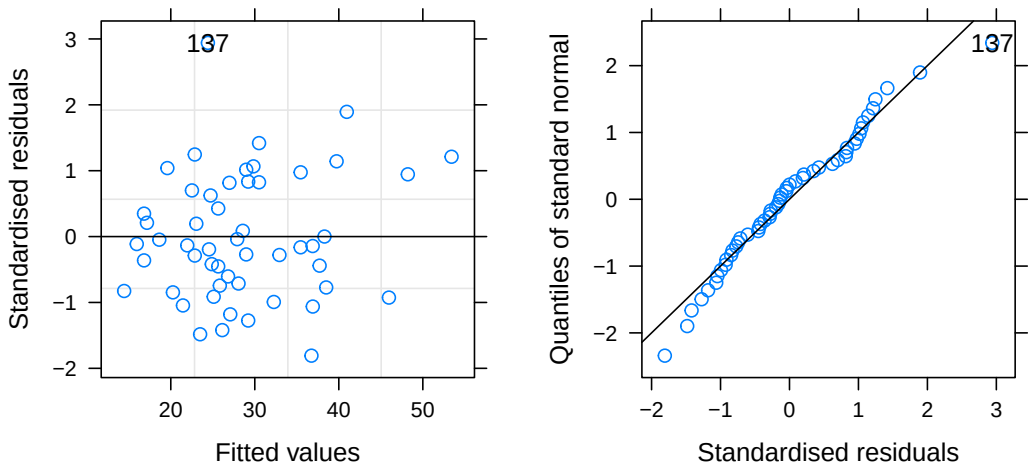


Figure 5.11: Final model (M30) ICU-FSS, rehabilitation activity and pressure support increment residuals. Patient 137 is outside the 95% confidence interval of the standardised residuals. Standardised residuals = residual/SD of all residuals. Quantities of standard normal are those values expected if the residuals were normally distributed.

	Rehab activity	ICU-FSS	M27	M28	M29	M30
Intercept	23.25***	14.74***	19.98**	14.89***	11.80**	11.88**
	(2.63)	(3.52)	(6.19)	(3.72)	(3.84)	(3.79)
STS or BCT	11.56**		−7.86	0.74	−1.48	−1.53
	(3.45)		(9.80)	(4.92)	(4.86)	(4.81)
ICU-FSS		1.14***	0.38	1.09**	1.20**	1.21**
		(0.25)	(0.80)	(0.38)	(0.38)	(0.37)
ICU-FSS:STS or BCT			0.90			
			(0.90)			
PS increment					1.44*	1.49*
					(0.67)	(0.63)
Prior rehabilitation					0.12	
					(0.49)	
AIC	414.25	406.21	409.16	408.19	406.41	404.48
BIC	422.06	414.02	420.87	417.95	420.07	416.19
Log Likelihood	−203.13	−199.11	−198.58	−199.10	−196.21	−196.24
Num. obs.	52	52	52	52	52	52
Num. groups	26	26	26	26	26	26

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$. BCT = bed chair transfer.

Table 5.11: Multilevel, multivariate, linear regression estimates and standard error of the means (SEM) for the percentage change in VO_2. The reference group for the rehabilitation actvity model is SOEB±balance exercises. M27 = Rehabilitation activity and ICU-FSS as an interaction term, the reference category is ICU-FSS:SOEB±balance exercises. M28 = Activity and ICU-FSS. M29 = Rehabilitation activity, ICU-FSS, PS increment and prior rehabilitation sessions. M30 = Rehabilitation activity, ICU-FSS and PS increment.

5.4 Changes in $\dot{V}O_2$ during rehabilitation activities performed by healthy individuals

A convenience sample of seven healthy, non-age or gender-matched individuals were recruited in order to draw comparisons against the patients' $\dot{V}O_2$ during rehabilitation activities *(Table 5.12)*. STS x1 was chosen as the rehabilitation activity to compare as it had the narrowest 95% confidence intervals for $\dot{V}O_2$ during rehabilitation activities. Also it was very difficult to record a $\dot{V}O_2$ change in normals for any activity less than STS x1, possibly due to the brevity of the sessions.

5.4.1 Method

The $\dot{V}O_2$ of the healthy subjects was measured using the MGU via a face mask. Subjects were requested to sit in a semi-recumbent position, 30° head-up until there was a <10% variation in resting $\dot{V}O_2$. They were then asked to SOEB, stand and then sit down and return to the semi-recumbent position.

5.4.2 Analysis

The healthy individuals' data were analysed in the same way as the patient data. As their data were not normally distributed, comparisons between patients and healthy individuals were performed using Wilcoxon signed rank tests of;

i) resting $\dot{V}O_2$ in mL.Kg.$^{-1}$min^{-1},

ii) total session VO_2 in mL.kg^{-1},

iii) rehabilitation VO_2 (total session VO_2 - resting VO_2),

iv) percentage change in VO_2.

Patient efficiency was calculated using healthy individuals as the reference category.

$$\text{Session power} = \text{Total session } VO_2 \text{ (mL.kg}^{-1}\text{)} \tag{5.4}$$

$$\text{Total session } VO_2 \text{ (mL.kg}^{-1}\text{)} = \textit{session } \dot{V}O_2 \ (mL.kg^{-1}min^{-1}) * \textit{session duration } (min)$$

$$\text{Rehabilitation power} = \text{Rehabilitation } VO_2 \text{ (mL.kg}^{-1}\text{)} \tag{5.5}$$

$$\text{Rehabilitation } VO_2 \text{ (mL.kg}^{-1}\text{)} = \textit{rehabilitation } \dot{V}O_2 \ (mL.kg^{-1}min^{-1}) * \textit{session duration } (min)$$

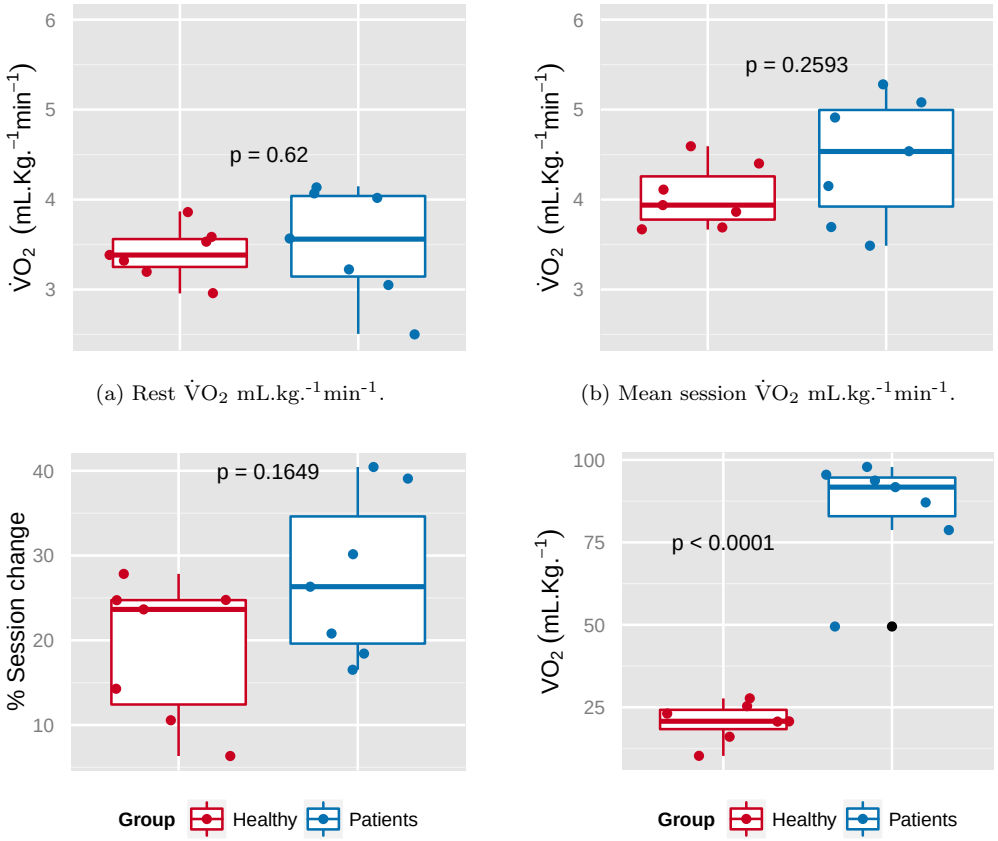
5.4.3 Results

There was a significant difference between the time taken for patients and healthy individuals to SOEB, stand and return to bed (*Table 5.12*). Box plots of resting $\dot{V}O_2$, total session VO_2

and rehabilitation VO_2 are shown in *Figure 5.12*.

Group	Number	Session Duration			Age		Weight (Kg)	
		Min	Median	Max	Mean	SD	Mean	SD
Healthy	7	02:48	05:38	07:02	34	4	70	17
Patients	7	10:55	18:32	26:19	68	11	80	12

Table 5.12: Time required to sit-to-stand for healthy volunteers and patients.



(a) Rest $\dot{V}O_2$ mL.kg.$^{-1}$min^{-1}.

(b) Mean session $\dot{V}O_2$ mL.kg.$^{-1}$min^{-1}.

(c) Percentage change in session VO_2.

(d) Session VO_2 mL.kg.$^{-1}$.

Figure 5.12: Healthy individual and patient $\dot{V}O_2$ during a sit-to-stand manoeuvre.

There was no statistical difference between the resting $\dot{V}O_2$ of the patients and healthy individuals (*Figure 5.12a*), the mean $\dot{V}O_2$ of the session (*Figure 5.12b*), or the percentage session change (*Figure 5.12c*). The Wilcoxon Signed Rank estimate of the difference in $\dot{V}O_2$ at rest was -0.177 mL.Kg.$^{-1}$min^{-1} (95% CI: -0.740 to 0.533 mL.kg.$^{-1}$min^{-1}) (p = 0.62). The estimate of the difference between the mean session $\dot{V}O_2$ was -0.482 mL.Kg.$^{-1}$min^{-1} (95% CI: -1.214 to 0.380 mL.kg.$^{-1}$min^{-1}) (p = 0.2593). The estimate of the difference between the patient and healthy percentage session change was -7.872% (95% CI: -19.59 to 5.218%) (p = 0.1649). There was a significant -68.69 mL.kg^{-1} (95% CI: -77.08 to -53.37 mL.kg^{-1}) (p = 0.0006) difference between the healthy volunteer and patient session VO_2 (mL.kg^{-1}). For

patients, efficiency for the whole session was 24.23% and for the rehabilitation component 19.43%. Patients consumed, on average, 4.12 times more oxygen to SOEB, stand and then return to bed compared to healthy individuals (95% CI: 0.82 to 17.07).

5.4.3.1 HR data

Heart rate data are the most often cited way to decide when to start and when to stop rehabilitation sessions [143, 146, 164]. However, a frequent oversight is that many patients are receiving rate limiting-drugs (RLD), such as beta-adrenergic blockers.

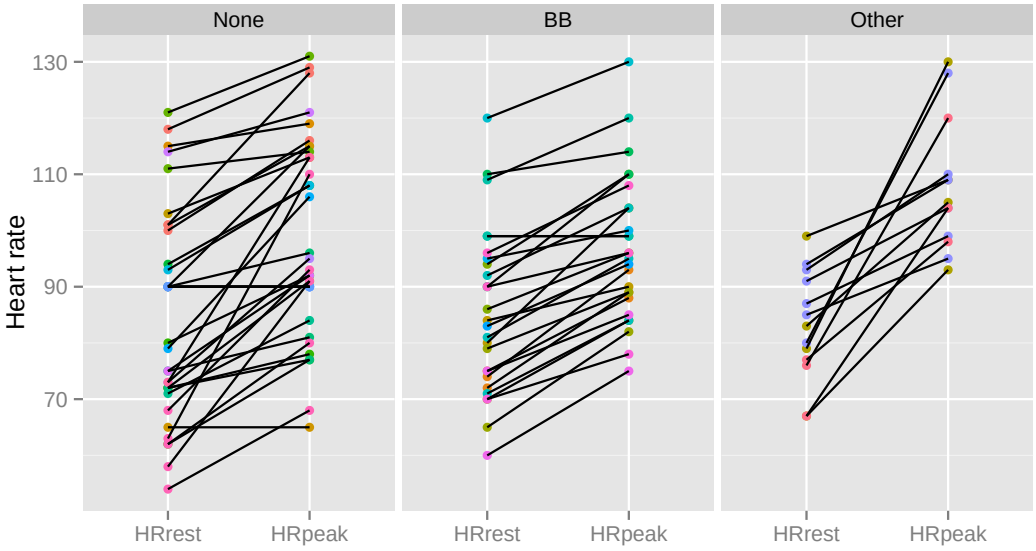
Analysis. As the data were normally distributed, unpaired Student's t-tests of the percentage change in heart rate, HRrest as a percentage of cHRmax, and HRpeak as a percentage of cHRmax were carried out in patients receiving beta-adrenoceptor blocker (BB) vs. no RLD as well as other RLD vs. no RLD.

Results. Of the 42 patients who were enrolled and had ≥1 exercise sessions recorded; 20 (48%) patients were receiving a rate-limiting drug (RLD); 16 (38%) were taking a beta-adrenoceptor blocker and 4 (10%) another rate limiting drug e.g digoxin or amiodarone. The resting and peak HR of the 33 patients who had both values recorded for ≥1 tests are plotted and grouped by the use of BB, other RLD or no RLD (*Figure 5.13a*). Three of the patients in the RLD group were in atrial fibrillation. The patients receiving a RLD had a greater percentage change in HR than the non-RLD patients with a 13.7 % (95 CI: 0.23 to 27.30 %) ($p = 0.046$) increase in heart rate (*Figure 5.13b*). There was a 6.75 % (95 CI: -0.4 to -13.10 %) ($p = 0.04$) increase in heart rate between the BB and non-RLD patients, with the non-RLD patients having a greater percentage increase in HR compared to the BB patients (*Figure 5.13c*). One-third of patients had resting heart rates >60% of their cHRmax (26% of BB, 31% of No RLD and 38% of other RLD patients) (*Figure 5.13d*). Twenty percent reaching a HRpeak >75% of their cHRmax (3% of BB, 20% of No RLD, and 50% of other RLD patients).

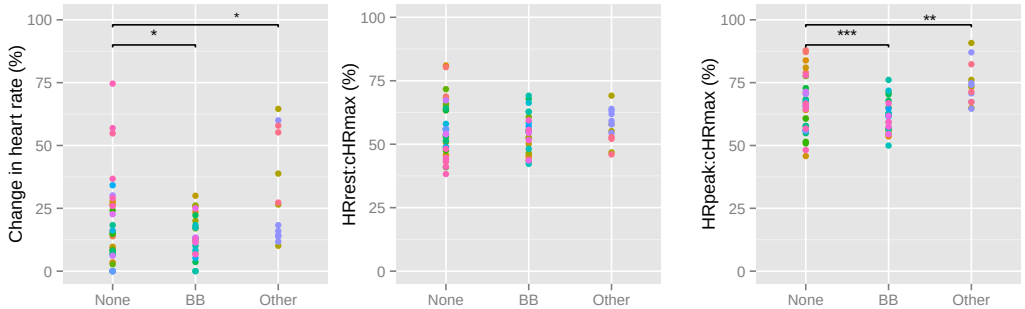
5.4.4 Discussion

5.4.4.1 Technique

Measuring $\dot{V}O_2$ during rehabilitation interventions in mechanically ventilated patients is technically challenging, time consuming and, given that 52 (41%) of the tests were unusable, frustrating *(Table 5.13)*. Depending on the rehabilitation activity, tests took between 1 and 2 hours, with a further 20-30 minutes to analyse each test. From a technical perspective, the instability of the F_iO_2 delivered by the *Servo i* ventilator resulted in data being inadequate in 10 (7%) of the sessions. Incompatibility of NHS security software and the driver for the MGU



(a) Heart rate changes with beta blocker(BB), none and other rate liming drugs.



(b) Percentage change in heart rate.

(c) Resting heart rate as a percentage of cHRmax.

(d) Peak heart rate as a function of cHRmax

Figure 5.13: Heart rate changes during rehabilitation.
***p <0.001, p ** <0.01, *p <0.05.

resulted in a further 14 (11%) tests being lost (six where there was no useful data and eight where there was incomplete patient recovery data). The written records of the session were inadequate in 8 (6%) tests, preventing retrospective identification of activity timings. Only five patients declined to continue a session once the equipment was set up. The remaining issues were most probably unavoidable or happened very infrequently; these included the need to increase the patient's F_iO_2, and persistent coughing. The time-consuming nature and unreliability of the technique in this patient group preclude its use in routine clinical monitoring of rehabilitation sessions.

5.4.4.2 Repeatability and sensitivity of the technique

It was not possible to test the repeatability of the measurements for either the cycle tests or the rehabilitation sessions. Patients were too fatigued at the end of a rehabilitation session to repeat the same activity. The few comparisons that were possible between different days were not valid comparisons due to changes in patients physiological status. There were insufficient

Reasons tests not analysed	Number
F_iO_2 increased during test	2
Flow sensor blocked during session	1
No recovery data	8
Patient coughing	2
Patient declined	5
Patient vomited no rehab	1
Unable to identify	8
Unstable F_iO_2	10
VO_2 erratic	7
Weaned	1
NHS firewall software	6
Withdrawn	1

Table 5.13: Reasons tests not analysed.

repeated tests over time to test the sensitivity of the tests to measure change over time.

Ergometry was chosen as an exercise stimulus as it was expected to be a standardisable method to quantify exercise load. Upper-limb, cycle ergometry was chosen as it was an exercise method that had previously been employed with success in a number of patients on the ICU. I anticipated that more patients would be able to cycle actively with their arms than their legs.

RPM. In order to generate comparable workloads both between and within patients a consistent pedal frequency (RPM) had to be generated on the ergometer. No currently published studies have sought to standardise this [128, 171]. 35 RPM was the minimum the manufacturer recommended for reliable comparisons of the Monarch ergometer. However, of the nine patients with $\dot{V}O_2$ data who cycled for $\geq$3 minutes, only 3 of them managed $\geq$35 RPM. From the manufacturers data, this suggests that these patients were working at 4 watts. Unfortunately at lower RPM's the work rate increases due to the need to overcome inertia of the ergometer. So it is likely that those patients with a low RPM were working harder than those with a high RPM. With respect to the anaerobic threshold calculations, 3 work rates were used (5, 10 and 15 watts) to estimate the anaerobic thresholds. Even a generous estimate of 15 watts suggests extremely low AT's. Estimating that, with the exception of one patient, all would have reached their AT by the equivalent of a healthy person standing (2 METS or 7 $mL.Kg.^{-1}min^{-1}$). However, it is not possible to exclude slow $\dot{V}O_2$ uptake kinetics as a reason

for not reaching a plateau in $\dot{V}O_2$ in the time course of the test. An unloaded ergometer with an accurate power output at low RPM's would be essential for any future study.

ICU-FSS cycling model. The association between physical function status (measured by ICU-FSS) and the ability to cycle for 3 minutes was not surprising. The odds of being able to cycle increased by 14% (95% CI: 0.003 to 27%) (p = 0.05) for every point increase in ICU-FSS. However, patient motivation can not be excluded as a confounder. The main reason patients gave for stopping the cycle session was"fatigued", rather than breathlessness. The way the patients were added to the model may also have influenced the estimates. Patients had between one and 5 cycle tests recorded each. No more than 2 tests per patient could be added to the model without one patient becoming overly influential. While it is not possible to get accurate estimation of patients' exercise capacity or intensity from this data, it does highlight how deconditioned patients are and how difficult it is to find ways to measure exercise capacity and intensity at very low levels of physical function.

Cycling recruitment. Between December 2011 and March 2013, 21 patients were recruited and 12 cycled. Between November 2013 and March 2015, 23 patients were recruited and 3 patients cycled. From November 2013 I was no longer working clinically on the ICU and relied on the ICU team for information on patients who were suitable to recruit and on their readiness to cycle. Additionally, as cycling was more labour intensive for the team, low staffing levels influenced the numbers of patients recruited who went on to cycle.

5.4.4.3 Rehabilitation.

Extrapolating from the the univariate regression analysis, including just the rehabilitation activity, SOEB increased a patient's $\dot{V}O_2$ from 3.5 mL.Kg.$^{-1}$min^{-1} to 4.29 (95% CI: 4.10-4.51mmL.Kg.$^{-1}$min^{-1}), while standing increased the $\dot{V}O_2$ to 4.72 mL.Kg.$^{-1}$min^{-1} (95% CI: 4.15-5.28 mL.Kg.$^{-1}$min^{-1}). These mean values for sitting and standing activities are under the estimated anaerobic thresholds for the six patients who performed the cycling tests (if a power output of 10 watts is assumed). The peak values of sitting and standing are considerably greater (*Table 5.14*). This suggests that patients may be exercising above their anaerobic threshold for at least part of their rehabilitation sessions. The importance of this requires further investigation.

Activity	n	Peak $\dot{V}O_2$ (mL.Kg.$^{-1}$min^{-1})			
		Mean	SD	Min	Max
Sitting	25	6.49	2.40	3.76	15.63
Standing	27	7.26	1.58	4.68	11.23

Table 5.14: Peak $\dot{V}O_2$ for sitting and standing activites

The large standard deviation of the sample data reflects not only the small sample size but also the heterogeneity of the patients recruited and the multiplicity of factors influencing energy expenditure during a rehabilitation session. The main factor that influenced the regression model was the patient's physical function status, rather than the actual rehabilitation activity. There are several plausible explanations for the relationship between ICU-FSS and the change in $\dot{V}O_2$. Less able patients may consume less O_2 because they are utilising less muscle, and/or, they have less muscle to recruit, and/or the muscle is less able to utilise O_2 due to bioenergetic failure or changes in fibre type composition as a result of ICUAW. It is likely to be a combination of these factors. While ICU-FSS in isolation might be associated with $\dot{V}O_2$, it does not help in estimating an individual patient's exercise capacity nor the intensity at which they are working.

The suggestion that an increment in ventilatory support could influence the change in $\dot{V}O_2$ further complicates the issue. It is not uncommon for ventilatory support to be increased during a rehabilitation session. The assumption is that off-loading the patient's mechanical respiratory load and/or reducing a patient's perception of breathlessness enables the patient to achieve more in a rehabilitation session. There is a trend towards an increase in rehabilitation duration for those patients who have their pressure support increased *(Figure 5.14)*. Why this happens is unclear. It may be that as the therapist has increased the ventilatory support, they push the patients harder or it may suggest that the perception of breathless or mechanical respiratory load are important manipulatable factors in mechanically ventilated patients. Further investigation into this process is warranted, but also challenging. It would necessitate a patient carrying out the same rehabilitation activity twice, once with no increase in the pressure support and again with an increase in support.

The regression analysis did not pick up any alteration in the percentage change in $\dot{V}O_2$ over time. This is likely due to insufficient numbers of patients repeating the same activity over time. Given the nature of rehabilitation in the ICU, patients were rehabilitated to their maximum functional level on each occasion. Ideally patients with high ICU-FSS scores would

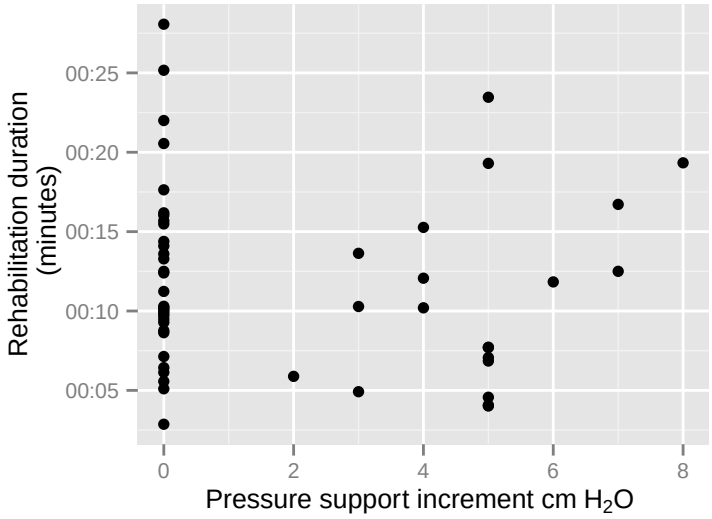


Figure 5.14: Pressure support increment and rehabilitation duration.

have had repeats of their low level activities to observe if the $\dot{V}O_2$ changed over time.

Patients vs. healthy individuals. One of the striking features of my findings was the difference in the time taken to stand between patients and healthy individuals. Patients took, on average, 3.5 times as long to stand and return to bed than healthy individuals. This mostly explains the quadruple decrease in session and rehabilitation efficiency VO_2 between the patients and healthy individuals.

5.4.4.4 HR measurement

The different heart rate response to exercise in BB, Non-RLD and RLD patients would suggest that heart rate is not a reliable or valid way to measure an exercise response in the majority of mechanically ventilated ICU patients. Additionally none of the heart rate variables added to to the regression model demonstrated an association with the percentage change in $\dot{V}O_2$.

5.4.4.5 Reasons for cessation of exercise

Unfortunately the reasons for ceasing exercise were not recorded for either the cycle or the rehabilitation sessions. This would have been an interesting variable to have collected and may have provided a useful insight into the limitations to exercise experienced by the patients.

5.4.5 Conclusion

Breath-by-breath gas exchange analysis provides valuable information regarding the patient's oxygen consumption during rehabilitation. However, it is not a practicable method for monitoring rehabilitation interventions in routine clinical practice.

Incremental tests to measure exercise capacity and intensity were not possible in this particular patient cohort. However, constant load tests are feasible for a subgroup of patients. This subgroup may be identifiable for future studies by their ICU-FSS.

Absolute exercise intensity, as measured by $\dot{V}O_2$, is not activity-dependent, highlighting the need to monitor individual patient's workload in real time. This need is intensified by the finding that some patients have AT's as low as 6-8 $mL.Kg.^{-1}min^{-1}$.

In future studies it would be useful to establish the reasons for cessation of exercise.

Given that it was not possible to use conventional methods to estimate exercise intensity, I decided to look at the possibility of estimating a patient's $\dot{V}O_2$ from other, more easily measured values. The starting point was the oxygen uptake efficiency slope (OUES).

Chapter 6

Potential methods of estimating oxygen consumption during rehabilitation of mechanically ventilated patients

The previous chapter illustrated that a specific rehabilitation activity, e.g. sitting over the edge of the bed, does not have the same oxygen cost for every patient, or indeed for an individual patient on different rehabilitation occasions. This highlights the need, at the very least, to identify the absolute intensity at which a patient is working and ideally, the intensity relative to an individual patient's maximum capacity. This would enable individualised exercise regimens to be created for patients and quantification of rehabilitation interventions.

During the BBGEA data collection, I noted how closely $\dot{V}_E$ mapped $\dot{V}O_2$ and that recovery of $\dot{V}_E$ to the pre-exercise state was indicative of the $\dot{V}O_2$ returning to baseline. However, while $\dot{V}_E$ could potentially be used as an indicator of recovery between exercise bouts during a rehabilitation session, the complexity of the relationship between $\dot{V}_E$ and $\dot{V}O_2$ currently negates its use as a direct estimate of absolute exercise intensity. The oxygen uptake efficiency slope (OUES) is a useful sub-maximal indicator of cardiorespiratory reserve, representing the absolute increase in $\dot{V}O_2$ associated with a 10 fold rise in $\dot{V}_E$ (*Equation 3.1*). The logarithmic transformation of $\dot{V}_E$ effectively linearises the relationship when $\Delta\dot{V}_E$ exceeds $\Delta\dot{V}O_2$ above the AT [176]. Although there is evidence that the exercise intensity at which the OUES is generated may also influence the slope [253], the OUES does provide a starting point for the development of a model to estimate $\dot{V}O_2$ from other, more readily available parameters.

6.1 Physiological rationale for model creation

A great deal of attention is now given to the relationship between $\dot{V}_E$ and $\dot{V}O_2$ [254], however there is a much clearer relationship between $\dot{V}_E$ and $\dot{V}CO_2$. As can be seen from *Equation 6.1*, alveolar ventilation ($\dot{V}_A$) is modified by both the P_aCO_2 set point and $\dot{V}CO_2$ (or metabolic load). That is, the higher the P_aCO_2 set point, the lower the required alveolar ventilation for a given $\dot{V}CO_2$, while the greater the metabolic load (greater $\dot{V}CO_2$) then the higher the required $\dot{V}_A$. The actual $\dot{V}_E$ necessary to maintain the P_aCO_2 set point is then modulated by the dead space:tidal volume ratio, i.e the greater the dead space:tidal volume ratio, the greater the $\dot{V}_E$ required to achieve the necessary alveolar ventilation for a given $\dot{V}CO_2$ and P_aCO_2 set point (*Equation 6.2*). This relationship is however confined to exercise between the initial kinetic phase and that occurring below the lactate threshold [255].

$$\dot{V}_A = \frac{863 * \dot{V}CO_2}{P_aCO_2} \tag{6.1}$$

$$\dot{V}_E = \frac{863 * \dot{V}CO_2}{P_aCO_2 * (1 - \frac{V_D}{V_T})} \tag{6.2}$$

Where 863 *is the correction for* $\dot{V}_E$ *to BTPS,*

$\dot{V}CO_2$ *to STPD and* CO_2 *as partial pressure.*

$$V_D = \frac{P_aCO_2 - P_{ET}CO_2}{P_aCO_2} \tag{6.3}$$

$$\dot{V}O_2 = \frac{\dot{V}CO_2}{RQ} \tag{6.4}$$

I did not have the contemporaneous P_aCO_2 and $P_{ET}CO_2$ values required to calculate dead space. Additionally, this model would require continuous $\dot{V}CO_2$ monitoring and knowledge of the RQ. This would generate multiple sources of error and two further variables to monitor.

Given that the only other option for gauging a patient's exercise intensity is the physiotherapist's best guess, in the absence of such data, I opted to establish whether modelling $\dot{V}O_2$ from $\dot{V}_E$ using resting $\dot{V}CO_2$ and resting $P_{ET}CO_2$ (both values are readily obtainable with a $P_{ET}CO_2$ monitor), was significantly inferior to estimating $\dot{V}O_2$ during rehabilitation by monitoring $\dot{V}CO_2$ and assuming a fixed RQ *(Equation 6.4)*.

Below the anaerobic threshold, $\dot{V}O_2$ and $\dot{V}CO_2$ are coupled by substrate metabolism. For the majority of patients, the RER[1] during rehabilitation is parabolic, starting high (usually around 1.1, presumably related to anxiety or possibly due to over-ventilation), dropping to a nadir of 0.7-0.8 during the exercise component of the session and returning to 1 during

[1]The ratio of CO_2 output to O_2 uptake per unit time. The RER reflects both the metabolic exchange of gases and transient changes in CO_2 and O_2 storage, hence RER can exceed RQ during hyperventilation where a greater volume of CO_2 is removed from the body than is produced.

recovery. This is similar to that seen in healthy individuals as a result of pre-test anxiety [256]. The mean RER of the analysable tests was 1.012 with a SD of 0.086. Clearly, this variability will introduce a significant bias. The relationship between resting $\dot{V}CO_2$, resting

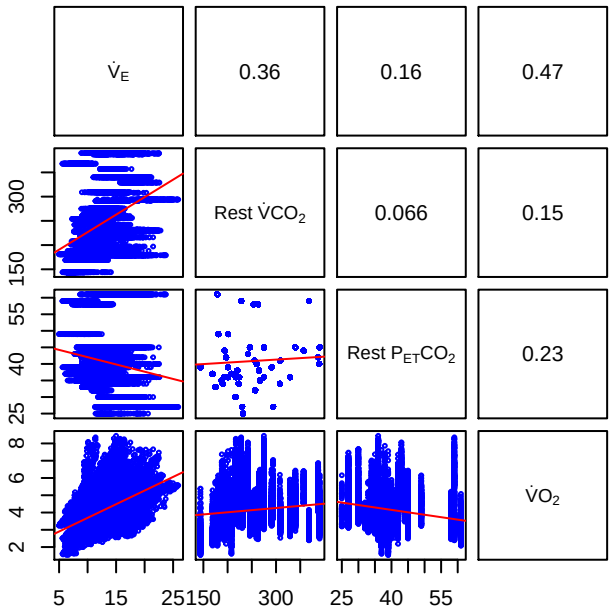


Figure 6.1: $\dot{V}_E$ model. Pairs plots. $\dot{V}_E$ in L.min^{-1}, Rest $\dot{V}CO_2$ in mL.min^{-1}, Rest $P_{ET}CO_2$ in mm Hg, $\dot{V}O_2$ in mL.Kg.$^{-1}$min^{-1}. The lower quadrant shows each variable plotted against the remaining variables, the upper quadrant provides the correlation coefficient for the corresponding lower quadrant. Highlighting a potential interaction between $\dot{V}_E$ and resting $\dot{V}CO_2$.

$P_{ET}CO_2$, $\dot{V}_E$ and $\dot{V}O_2$ are plotted in pair plots in *Figure 6.1*. There is a trend towards a greater exercise $\dot{V}_E$ values with higher resting $\dot{V}CO_2$. In the absence of the P_aCO_2 set point, it is not clear whether for some patients this increase in $\dot{V}_E$ is due to a lower P_aCO_2 set point or a higher metabolic rate ($\dot{V}CO_2$). $P_{ET}CO_2$, which is often used as an indicator of P_aCO_2 in clinical practice, has an anticipated negative correlation with exercise $\dot{V}_E$, i.e. as resting $P_{ET}CO_2$ increases, exercise $\dot{V}_E$ tends to decrease. However, again in the absence of a P_aCO_2 value, it is not clear whether for some patients this lower exercise $\dot{V}_E$ is due to a higher P_aCO_2 set point or a lower dead space (*Equation 6.3*). The purpose of including resting $\dot{V}CO_2$ and $P_{ET}CO_2$ was therefore not to influence the estimate of the slope but to explain some of the variation in the intercepts both within and between patients.

6.2 Rehabilitation data segment definitions

It was unclear how the choice of different segments of the rehabilitation sessions would influence the final regression models. The segment of the rehabilitation data to be used for both models required an even spread of values in each of a low, medium and high category, to prevent

excessive representation of high or low values. For the $\dot{V}_E$ model, the data needed to have acceptable agreement between $\dot{V}O_2$ and $\dot{V}_E$. Therefore, the segments of the rehabilitation sessions were labelled as *(Figure 6.2)*:

Segment a: all data,

Segment b: all rehabilitation data,

Segment c: exercise-only rehabilitation data, excluding rest data between parts of the rehabilitation sessions, and

Segment d: incremental data only.

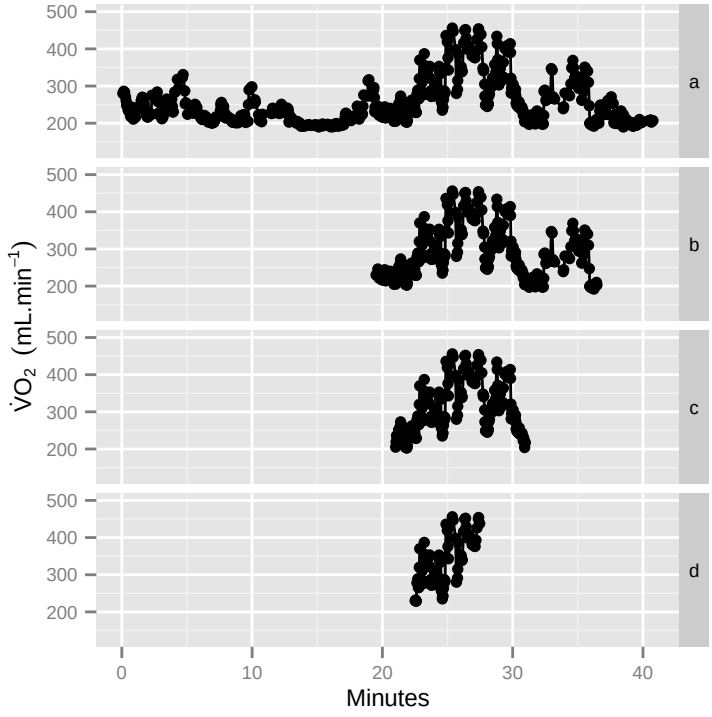


Figure 6.2: Example of rehabilitation data segments. (a) = all data, (b) = all rehabilitation data, (c) = exercise only rehabilitation data, excluding rest data between parts of the rehabilitation sessions, and (d) = incremental data only.

In order to decide which segment of the data to use, I collated the number of data points for each segment *(Table 6.1)*. I then plotted $\dot{V}O_2$ against $\dot{V}_E$ for each segment with computation of the corresponding linear regression line, coefficient estimate for $\dot{V}_E$ and r^2 value *(Figure 6.3)*. Segment b provided the most even spread of data points. Segment b also lost fewer datasets when using an $r^2 \geq 0.45$ cut off for the $\dot{V}O_2$:$\dot{V}_E$ relationship. The standard deviation of the estimates of the coefficient for $\dot{V}_E$ was also smaller in segment b than in the other segments.

I did this work with a view to being able to create a model to estimate $\dot{V}O_2$ during rehabilitation, given a future bigger sample size. The following sections aim to explore the relationship between $\dot{V}CO_2$ and $\dot{V}O_2$ and between $\dot{V}_E$ and $\dot{V}O_2$ during the rehabilitation of mechanically ventilated patients.

Segment	Low (<3.5 mL.Kg.$^{-1}$)	Medium (3.5-4.4 mL.Kg.$^{-1}$min^{-1})	High (≥4.5 mL.Kg.$^{-1}$min^{-1})
a	22083	20855	14286
b	10168	12889	11051
c	2015	6529	7188
d	433	2077	1946

Table 6.1: Data counts for each rehabilitation segment.

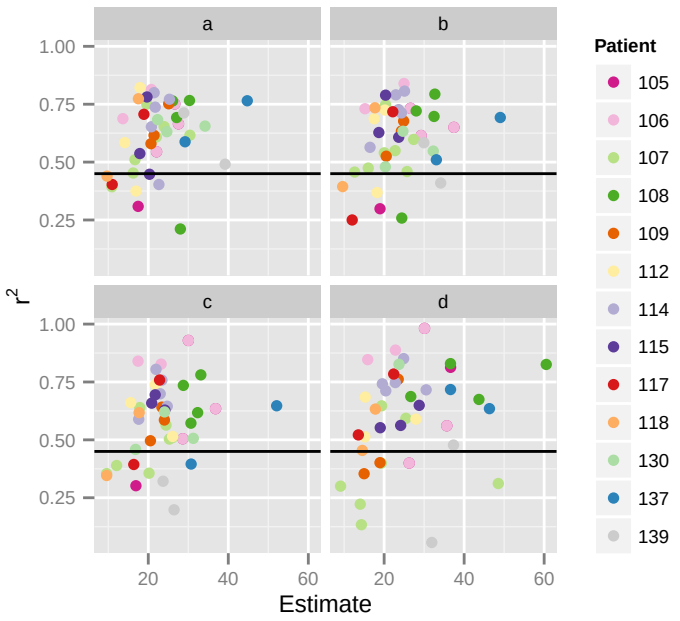
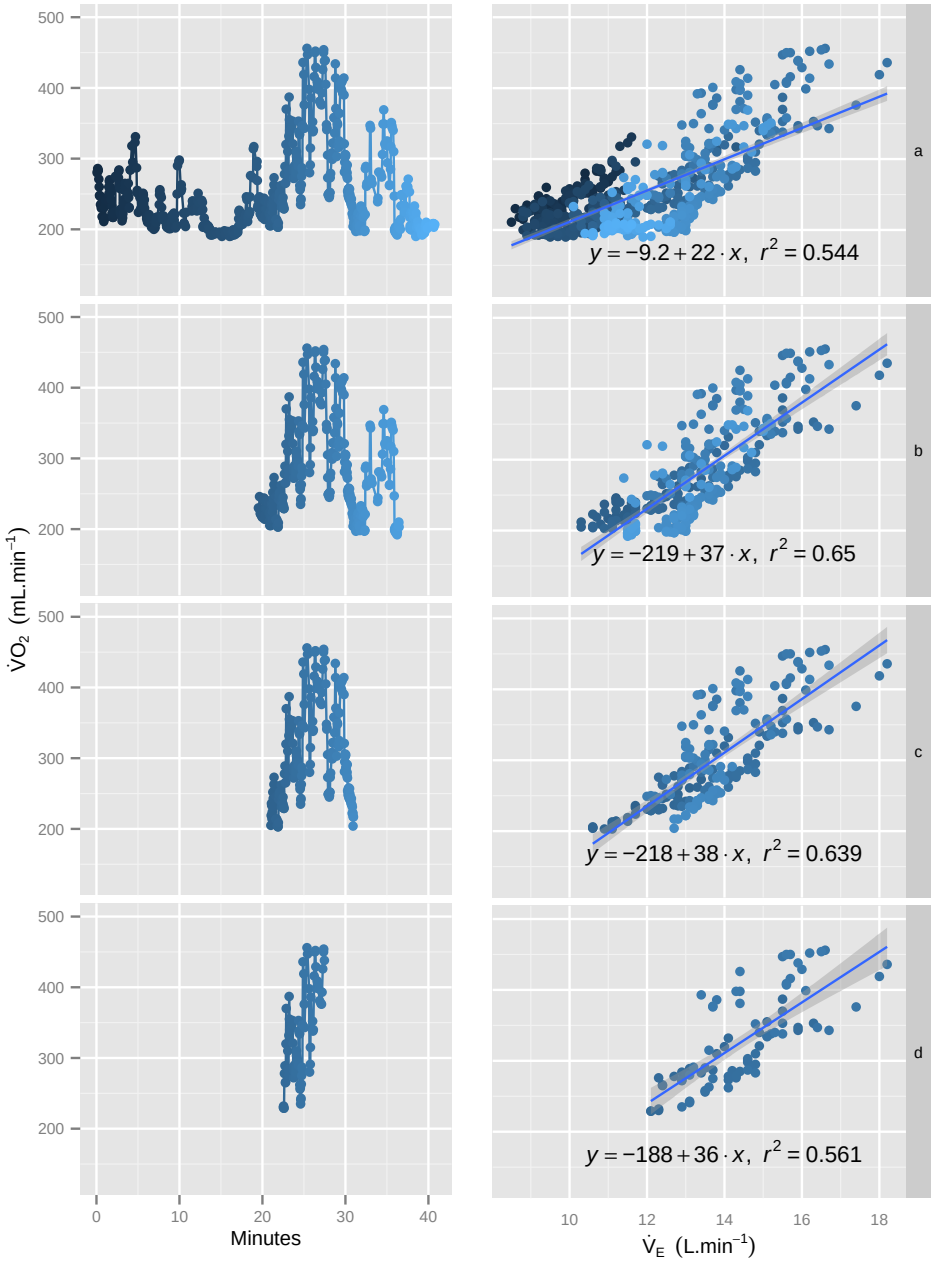


Figure 6.3: Rehabilitation data segments (panels a,b,c and d), with regression estimated coefficients of $\dot{V}O_2$ vs. $\dot{V}_E$ plotted against the corresponding r^2 value. A cut point of $r^2 \geq 0.45$ is shown.



(a) Rehabilitation segments. $\dot{V}O_2$ vs. time.

(b) Rehabilitation segments. $\dot{V}_E$ vs. $\dot{V}O_2$.

Figure 6.4: Example of data segments. (a) = all data, (b) = all rehabilitation data, (c) = exercise only rehabilitation data, excluding rest data between parts of the rehabilitation sessions, and (d) = incremental data only. The shading of the data points corresponds in each of the panels, illustrating the origin of the $\dot{V}_E$ vs. $\dot{V}O_2$ data points in the rehabilitation session.

6.2.1 Glossary of statistical terms

Multilevel linear mixed effects modelling. A form of regression analysis describing the relationship between a response or dependent variable and covariates that have been measured or observed along with the response, while allowing grouping of the data by a categorical covariate.

Random effects. Categorical covariates representing the observational units; in this instance patients or sessions. They are randomly sampled from a population of all levels being studied.

Fixed effects. Parameters associated with the particular levels of a *random effect*, they can be categorical or continuous.

Caterpillar plots. A method of visualising the *random effects* of a *multilevel mixed effects model*. They illustrate the distance the estimate of the intercept of the individual levels lie from the estimate of the intercept of the whole model.

Residuals. The difference between the calculated values from the model and the actual observed values. They are often standardised as the residual divided by the the standard deviation of all the residuals.

QQnorm plots. A visual comparison of 2 probability distributions. In this case the QQnorm plot is used to evaluate the normality of the residual distributions. If the residuals are normally distributed they will lie on the x=y line.

Confusion matrices (or contingency tables). Display the proportion of values that are categorised by the predicted class (in columns), while each row represents the proportion in the actual class.

Collinearity. A phenomenon where covariates in a multiple regression model are highly correlated, such that one can be predicted from the other. In this situation the coefficient estimates of the multiple regression may change erratically in response to small changes in the model or the data.

Interaction terms. Terms that are added to a model if two covariates affect the response variable in a way that is non-additive.

6.2.2 Principles of model development

The data collected from the rehabilitation and cycle sessions is hierarchical; each patient has multiple sessions, each session has multiple data points. Therefore modelling the data using a single linear model e.g. $y=ax+b$, not only violates the assumption of independence between

observations, but risks the Simpsons paradox where "erroneous conclusions can be drawn if grouped data, drawn from heterogeneous populations are collapsed and analysed as if from a single population" [257]. An alternative approach is to create separate linear models for each patient or each session e.g. $y=a_n+b_n$ where n is the number of patients or sessions. However this does not allow a clear summary of the results.. Multilevel linear mixed effects modelling allows resolution of non-independence by assuming a different "baseline" (intercept) response variable value (in this case $\dot{V}O_2$) for each patient or session (level).

Multilevel linear mixed effects modelling is a form of regression analysis describing the relationship between a response or dependent variable and covariates that have been measured or observed along with the response, while allowing grouping of the data by a categorical covariate. These categorical covariates represent observational units; in this instance patients or sessions. They are randomly sampled from a population of all levels being studied and are known as *random effects*. The parameters associated with the particular levels of a *random effect* are *"fixed effects"* and can be categorical or continuous.

In the first instance it is necessary to ensure that the extent of the between-group variability is sufficient to warrent incorporation as a *"random effect"*. This is done by estimating the variance around the "baseline" (intercept) response variable value (in this case $\dot{V}O_2$) when the data is grouped. If there is no variance between groups then the *"random effect"* should not be included. The *"random effects"* can be further visualised by caterpillar plots, which plot the distance for each individual patient the estimated "baseline" (intercept) is from the estimated model "baseline" (intercept). The impact on the estimated intercept of adding *"fixed effects"* to the model can be also be visualised.

Once the final model has been selected then the *residuals* of the model can then used to analyse how well the overall model fits each individual patient or session. These are usually plotted as *standardised residuals*. Plotting the residuals against the individual covariates allows visualisation of any bias or non-linear relationship that has been introduced. Finally QQnorm plots can be used to evaluate the normality of the residuals. If the residuals do not follow a normal distribution, this might indicate that one or more of the covariates is not linearly related to the response variable.

6.3 Using $\dot{V}CO_2$ as an estimate of $\dot{V}O_2$

6.3.1 $\dot{V}CO_2$ model creation

6.3.1.1 Method

Data from 48 sessions in 19 patients, where there was a mean RER of <1.1, were added to a linear-mixed effects multilevel model [248]. The random effects of the model were selected first. In model RE1 each patient is allowed their own intercept while in RE2 each patient and each session have their own intercept (*Table 6.2*). All variables with a statistically significant linear association ($p<0.05$) with the dependent variable ($\dot{V}O_2$ measured in $mL.Kg.^{-1}min^{-1}$), were added to the model as the fixed terms (*Table 6.3*).

Caterpillar plots were created to illustrate the distance, the estimate of each coefficient of the intercept for both each patient, or session, lie from the estimated coefficient of the intercept for the the empty model (RE2) (*Figure 6.6a*) and the final model (M4) (*Figure 6.6b*).

The final model (M4) residuals were first visualised with a QQnorm plot[2] (*Figure 6.7*). *Figure 6.8* shows the residuals with respect to the patient and *Figure 6.9* with respect to the particular rehabilitation session. Then the model residuals were plotted against the fitted values (*Figure 6.10a*), weight (*Figure 6.10b*), $\dot{V}CO_2$ (*Figure 6.10c*) and RER (*Figure 6.10d*).

6.3.1.2 Interpretation of $\dot{V}CO_2$ model

The session, nested within the patient as the random effects of the model, substantially decreases the variance of both the intercept and the residuals of the model (*Table 6.2*). $\dot{V}CO_2$, age, and weight were the only factors univariately associated ($p<0.05$) with $\dot{V}O_2$ (*Table 6.3*). All variables entered into the model were essentially normally distributed. However, $\dot{V}O_2$ and $\dot{V}CO_2$ are somewhat left-skewed with age right-skewed with RER *(Figure 6.5).*

For every 100 $mL.min^{-1}$ increase in $\dot{V}CO_2$ there is a 0.012818 $mL.Kg.^{-1}min^{-1}$ increase in $\dot{V}O_2$. For every Kg increase in body mass there is a 0.008 $mL.Kg.^{-1}min^{-1}$ decrease in $\dot{V}O_2$. For every year increase in age there is a 0.055 $mL.Kg.^{-1}min^{-1}$ decrease in $\dot{V}O_2$. Interestingly, the variance of the random effect patient is zero suggesting that, in this instance, the random effect of the patient is redundant (*Table 6.4, M4*).

As can be seen from *Figure 6.8*, patient 137 and 134 contribute considerably towards the

[2]QQnorm plots illustrate the residuals plotted against the expected residuals if they were normally distributed.

residuals. Patient 137 was the heaviest patient at 109 Kg, but also had the highest peak $\dot{V}CO_2$ values (not adjusted for weight). Session 117 *(Figure 6.9)* for patient 134 had an RER towards the lower end of the dataset.

The residuals increase as RER increases above 1 and as RER decreases below 1. There is less accuracy for low RER than high RER values (*Figure 6.10b*). Thus, as expected, assuming a common RER introduces a significant bias.

The standardised residuals plotted against $\dot{V}CO_2$ (*Figure 6.10d*) show that for $\dot{V}CO_2$ values above 550 mL, the residuals increase considerably. These high values may be due to patients exercising above their AT, where the relationship between $\dot{V}O_2$ and $\dot{V}CO_2$ is not linear. Further corroboration with lactate values is required to establish this.

The heavy tailed QQnorm plot shows a non-normal distribution (*Figure 6.7*). This suggests that either patients 134 and 137, for whom the biggest residuals are apparent, are significant outliers or that there is not a linear relationship between the fixed effects (weight, age and $\dot{V}CO_2$) and $\dot{V}O_2$. Simple measures such as logarithmic transformation of the independent variables do little to normalise the residuals.

Removing patients 134 and 137 from the model significantly reduces the residuals but has little impact on the overall model estimates. *(Figure 6.11 and Table 6.4, M5).*

The simulation of values (n = 50) and the 95% confidence intervals [17] that could be expected from the final $\dot{V}CO_2$ model (M4) are shown in *Figure 6.12*. This illustrates that predicted values have a wide confidence interval.

	RE1	RE2
(Intercept)	4.33***	4.34***
	(0.18)	(0.17)
AIC	50426.88	45073.49
BIC	50450.77	45105.35
Log Likelihood	−25210.44	−22532.74
Num. obs.	21276	21276
Num. patients	19	19
RE variance: patient	0.62	0.42
Residual variance	0.62	0.48
Num. sessions		48
RE variance: session		0.26

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 6.2: Random effects for $\dot{V}CO_2$ modeling sample. RE1 = Patient, RE2 = Patient and Session. AIC = Akaike's information criterion, BIC = Bayesian information criterion, RE = Random effect, refering to the grouping structure; patient or session.

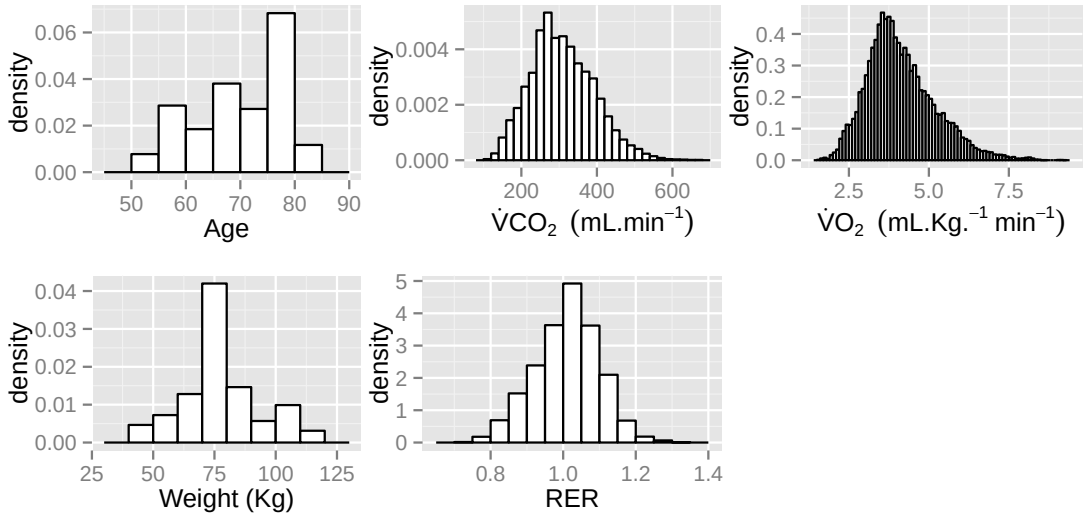
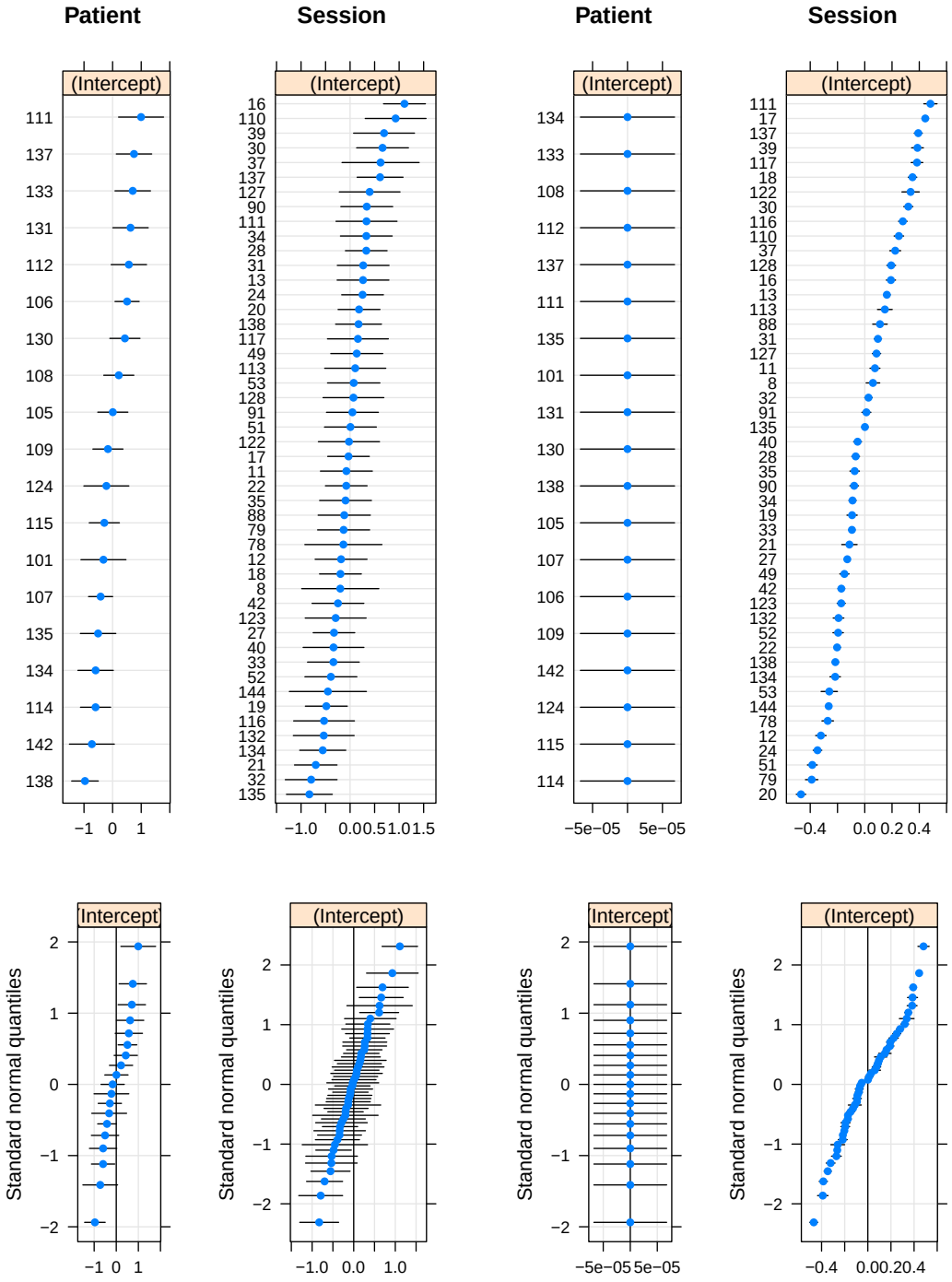


Figure 6.5: $\dot{V}CO_2$ model. Histograms of dependent and independent variables and RER. $\dot{V}O_2$ and $\dot{V}CO_2$ are left skewed and age right skewed with RER.

	RE2	M1	M2	M3	M4
Intercept	4.339***	0.307	4.316***	1.507	4.886***
	(0.169)	(0.230)	(0.190)	(1.462)	(0.302)
$\dot{V}CO_2$		12.812***	12.820***	12.812***	12.818***
		(0.048)	(0.048)	(0.048)	(0.048)
Weight			−0.054***		−0.055***
			(0.002)		(0.002)
Age				−0.018	−0.008*
				(0.021)	(0.004)
AIC	45073.490	14159.406	14099.174	14160.727	14096.733
BIC	45105.351	14199.233	14146.966	14208.519	14152.491
Log Likelihood	−22532.745	−7074.703	−7043.587	−7074.363	−7041.367
Num. obs.	21276	21276	21276	21276	21276
Num. sessions	48	48	48	48	48
Num. patients	19	19	19	19	19
RE variance: session	0.261	0.057	0.059	0.057	0.061
RE variance: patient	0.418	0.972	0.008	0.939	0.000
Residual variance	0.480	0.112	0.112	0.112	0.112

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, $^{\cdot}p < 0.1$

Table 6.3: $\dot{V}CO_2$ model. RE2 = Random effects (patient and session) only, M1 = $\dot{V}CO_2$ (L), M2 = $\dot{V}CO_2$ (L) and weight (Kg). M3 = $\dot{V}CO_2$ (L) and age, M4 = $\dot{V}CO_2$ (L), age and weight (Kg). AIC = Akaike's information criterion, BIC = Bayesian information criterion. RE = Random effect, refering to the grouping structure; patient or session.



(a) Model RE2. Patient and session as random effects.

(b) Model M4. Patient and session as random effects, $\dot{V}CO_2$, age and weight as fixed effects.

Figure 6.6: $\dot{V}CO_2$ model. Random effects. Caterpillar plots to illustrate the distance, the estimate of the coefficient of the intercept for each patient, or session, lie from the estimated coefficient of the intercept for (a.) the empty model and (b.) the final model.

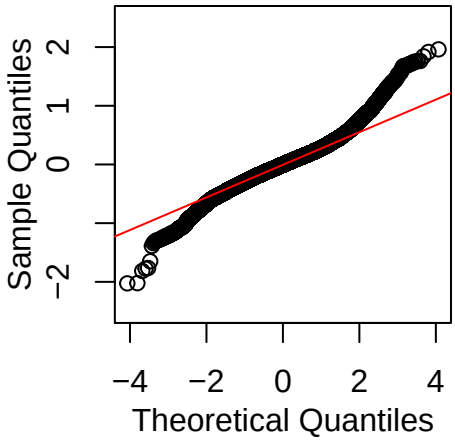


Figure 6.7: $\dot{V}CO_2$ model. QQnorm of $\dot{V}CO_2$ model. Illustrating the actual residuals plotted against the expected residuals if they were normally distributed. The residuals should lie along the straight line.

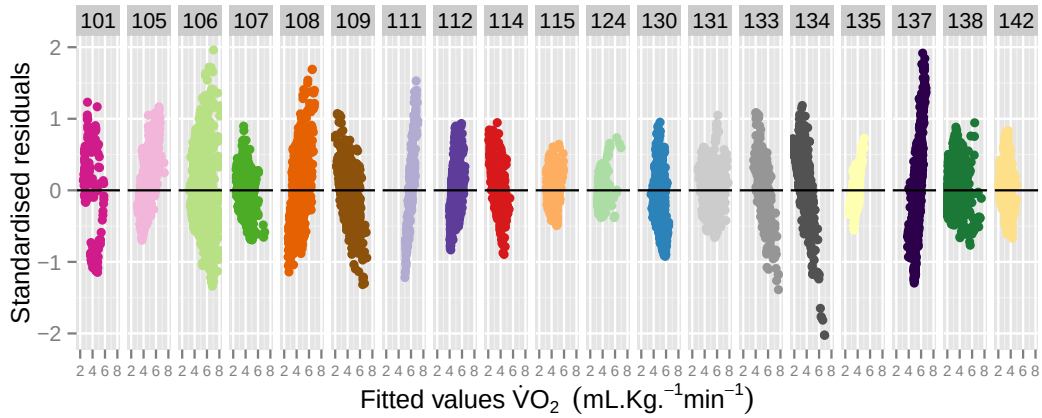


Figure 6.8: $\dot{V}CO_2$ model. Standardised residuals by patient.
Standardised residuals = residual/SD of all residuals. Thus illustrating how far the estimates lie from the actual values for each patient.

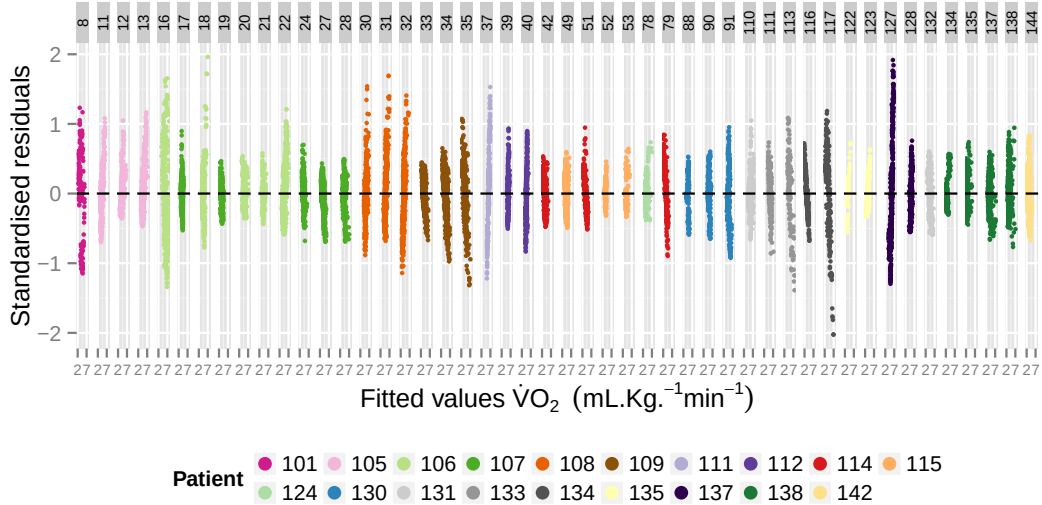


Figure 6.9: $\dot{V}CO_2$ model. Standardised residuals by session. Standardised residuals = residual/SD of all residuals. Thus illustrating how far the estimates lie from the actual values for each session.

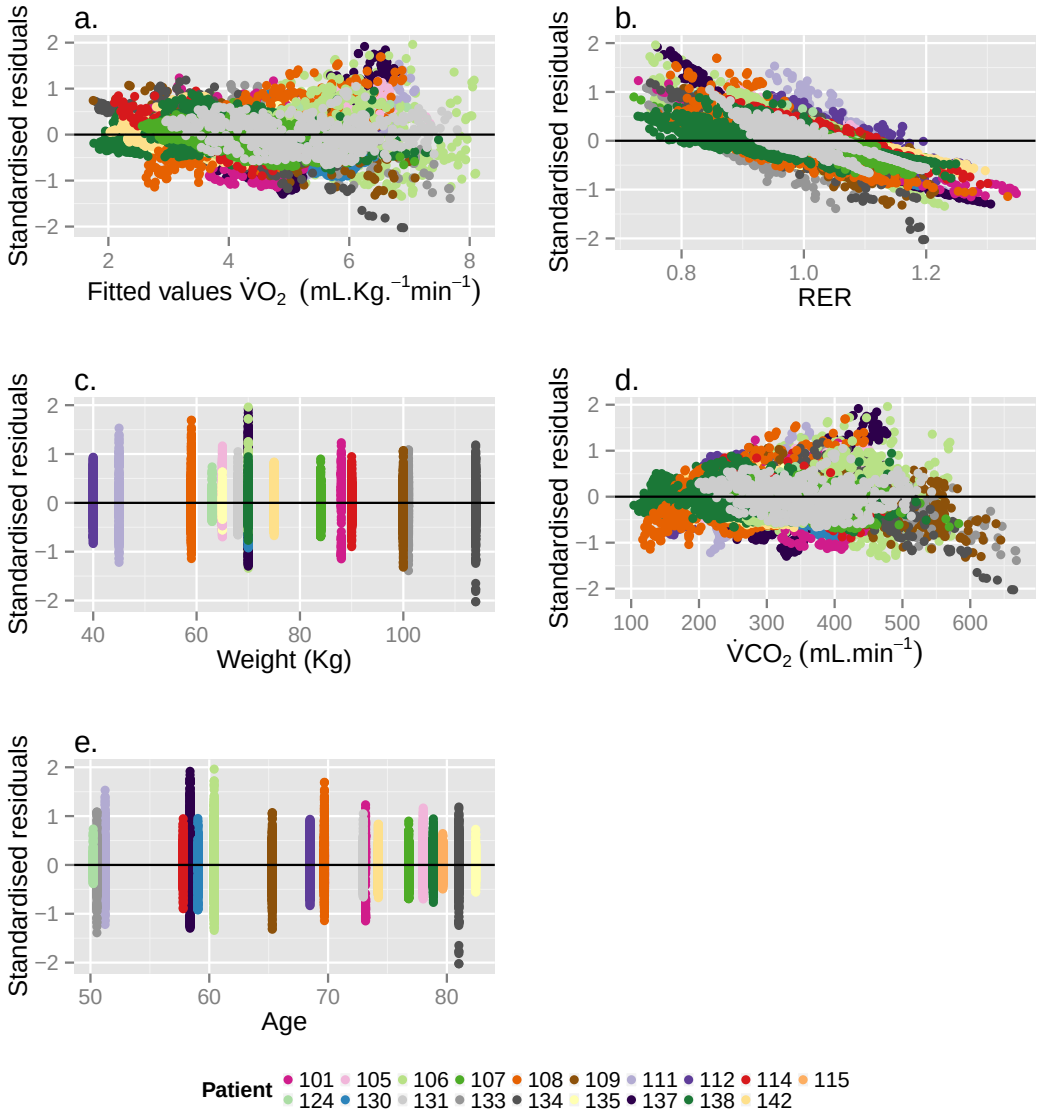


Figure 6.10: $\dot{V}CO_2$ model. Exploration of standardised residuals, plotted against (a). Fitted values, (b). RER, and the independent variables (c). weight, (d). $\dot{V}CO_2$ and (e). age. There is no observable bias with the fitted values, weight or age but RER and $\dot{V}CO_2$ demonstrate some bias.

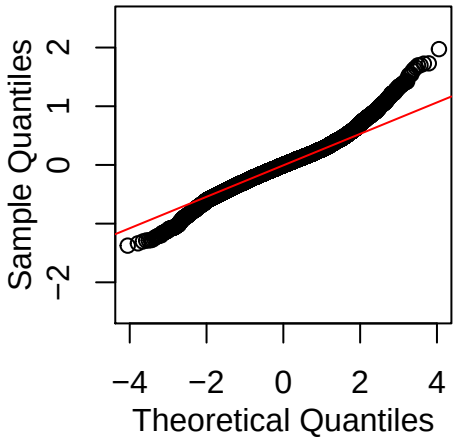


Figure 6.11: $\dot{V}CO_2$ model with 134 and 137 removed. QQnorm. Illustrating the actual residuals plotted against the expected residuals if they were normally distributed. The residuals should lie along the straight line.

	M4	M5
Intercept	4.886***	5.244***
	(0.302)	(0.349)
$\dot{V}CO_2$	12.818***	12.753***
	(0.048)	(0.047)
Weight	−0.008*	−0.010**
	(0.004)	(0.004)
Age	−0.055***	−0.057***
	(0.002)	(0.003)
AIC	14096.733	10426.050
BIC	14152.491	10481.284
Log Likelihood	−7041.367	−5206.025
Num. obs.	21276	19742
Num. sessions	48	44
Num. patients	19	17
RE variance: session	0.061	0.058
RE variance: patient	0.000	0.000
Residual variance	0.112	0.098

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 6.4: $\dot{V}CO_2$ model. M4 = with and M5 = without patients 134 and 137. AIC = Akaike's information criterion, BIC = Bayesian information criterion. RE = Random effect, refering to the grouping structure; patient or session.

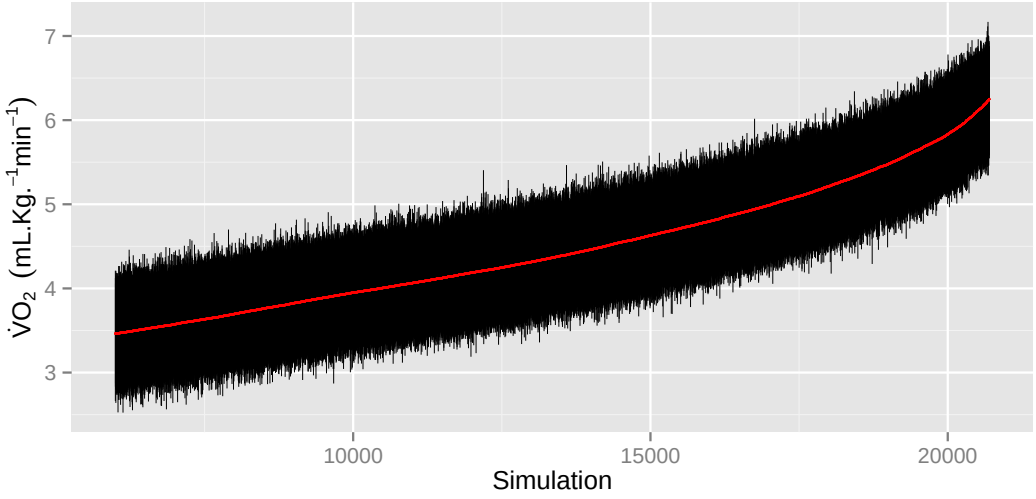


Figure 6.12: $\dot{V}CO_2$ model. Simulated values and 95% confidence interval.

6.3.1.3 Categorising the $\dot{V}CO_2$ model into three and four factors

Leaving aside the sample size that the model is derived from, the clinical utility of a continuous scale is limited. In practice it may be easier to work with a categorised low, medium or high intensity paradigm. This provides a range of values that a patient should work within to exercise at a categorised intensity.

The reference (actual) and predicted (model) $\dot{V}O_2$ values were classified as low (<3.5 mL.Kg.$^{-1}$min^{-1}), mid (3.5-4.4 mL.Kg.$^{-1}$min^{-1}) and high ($\geq$4.5 mL.Kg.$^{-1}$min^{-1}) workloads *(Table 6.5)*. A confusion matrix[3] was created *(Figure 6.13)* and multi-group receiver operated characteristic (MROC) [14] values calculated for the ability of the model to predict the actual $\dot{V}O_2$ values. Similarly, this was done again, this time creating four categories, low (<3.5 mL.Kg.$^{-1}$min^{-1}), mid (3.5-4.24 mL.Kg.$^{-1}$min^{-1}), high (4.25-4.9 mL.Kg.$^{-1}$min^{-1}) and very high ($\geq$5 mL.Kg.$^{-1}$min^{-1}) workloads *(Table 6.7)*.

Stratification of the $\dot{V}CO_2$ model into three categories (low, mid and high), has positive predictive values (PPV) of 0.87, 0.82 and 0.86 respectively and negative predictive values (NPV) of 0.95, 0.87 and 0.95 respectively *(Table 6.6)*. The overall multi-class area under the curve is 97.45%. With four categories (low, mid, high and very high), the PPV is 0.87, 0.76, 0.64 and 0.84 respectively and NPV is 0.95,0.87, 0.82 and 0.97 respectively *(Table 6.8)*. The multi-class area under the curve is 96.42%.

While the three category model has remarkably good predictive performance, how useful and easy it is to use in the clinical setting remains to be investigated. The four category model, which would probably be more useful in the clinical setting, performs well at the extremes but less well at defining the mid-range values. The three category model is thus more accurate than the four category model but probably has less clinical utility, as three categories would offer limited flexibility for exercise prescription.

[3]Confusion matrices display the proportion of values that are categorised by the predicted class (in columns), while each row represents the proportion in the actual class. The right diagonal represents the ideal.

Class	Category	Range ($mL.Kg.^{-1}min^{-1}$)
1	Low	<3.5
2	Mid	3.5-4.4
3	High	≥4.5

Table 6.5: $\dot{V}CO_2$ model. Three categories.

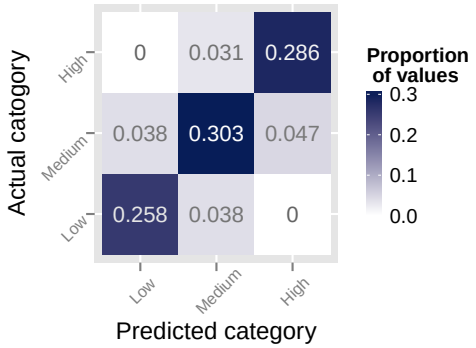


Figure 6.13: $\dot{V}CO_2$ model. Confusion matrix three categories.

	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value	Prevalence	Detection Rate	Detection Prevalence	Balanced Accuracy
Low	0.87	0.95	0.87	0.95	0.30	0.26	0.30	0.91
Medium	0.78	0.89	0.82	0.87	0.39	0.30	0.37	0.83
High	0.90	0.93	0.86	0.95	0.32	0.29	0.33	0.92

Table 6.6: Performance of $\dot{V}CO_2$ model with three categories.

Class	Category	Range ($mL.Kg.^{-1}min^{-1}$)
1	Low	<3.5
2	Mid	3.5-4.24
3	High	4.25-4.9
4	Very high	≥5 $mL.Kg.^{-1}min^{-1}$

Table 6.7: $\dot{V}CO_2$ model. Four categories.

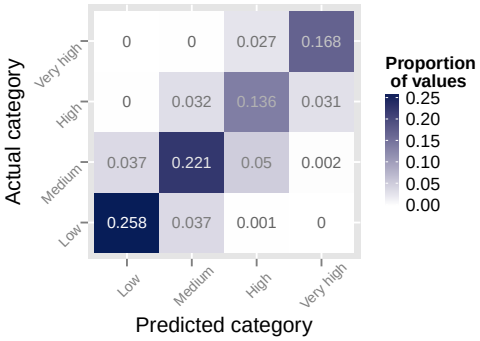


Figure 6.14: $\dot{V}CO_2$ model. Confusion matrix four categories.

	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value	Prevalence	Detection Rate	Detection Prevalence	Balanced Accuracy
Low	0.87	0.95	0.87	0.95	0.30	0.26	0.30	0.91
Medium	0.71	0.90	0.76	0.87	0.31	0.22	0.29	0.81
High	0.68	0.90	0.64	0.92	0.20	0.14	0.21	0.79
Very high	0.86	0.96	0.84	0.97	0.20	0.17	0.20	0.91

Table 6.8: Performance of $\dot{V}CO_2$ model with four categories.

6.4 Using $\dot{V}_E$ as estimate of $\dot{V}O_2$

6.4.1 $\dot{V}_E$ model creation

Forty-four datasets from nineteen patients, with a $\dot{V}_E$:$\dot{V}O_2$ r^2 >0.45 were used to create the $\dot{V}_E$ model. The random effects were evaluated first. The interactions between $\dot{V}_E$ and $P_{ET}CO_2$ and $\dot{V}_E$ and $\dot{V}CO_2$ were evaluated. This was done as there was significant collinearity between $\dot{V}_E$ and resting $P_{ET}CO_2$, and between $\dot{V}_E$ and resting $\dot{V}CO_2$ *(Figure 6.1)*. All variables with a statistically significant ($p<0.05$) linear association with the dependent variable ($\dot{V}O_2$), were added to the model as the fixed terms. REMB is the empty model with patient and session as random effects*(Table 6.9)*. There was a significant interaction between $\dot{V}_E$ and $\dot{V}CO_2$ (MB3d) and between $\dot{V}_E$ and $P_{ET}CO_2$ (MB3b), *(Table 6.10)*, chi-squared $p<0.0001$. Therefore both were added to the model as fixed effect interaction terms (MB3e). Age and weight were added to the model as the fixed terms (MB5c), *(Table 6.11)*. Gender was also added as the OUES has been demonstrated to be gender-specific [243]. However, as can be seen from *Table 6.11*, gender makes little difference to this model (MB5d). Histograms of $\dot{V}_E$, age, $\dot{V}O_2$ and weight show an essentially normal distribution *(Figure 6.15)*.

6.4.1.1 $\dot{V}_E$ model interpretation.

Therefore, in the final model (MB5c), for every;

- L.min^{-1} increase in $\dot{V}_E$ there is a 0.54 (95% CI: 0.52-0.55) increase in $\dot{V}O_2$ (measured in mL.Kg.$^{-1}$min^{-1}).
- mm Hg increase in resting $P_{ET}CO_2$ there is a 0.08 (95% CI: 0.05-0.11) increase in $\dot{V}O_2$ (mL.Kg.$^{-1}$min^{-1}), for every mm Hg increase in resting $P_{ET}CO_2$ there is a 0.01 (95%CI-0.01 to -0.01) multiplied by $\dot{V}_E$ (L) decrease in $\dot{V}O_2$.
- mL increase in resting $\dot{V}CO_2$, there is a 0.01 (95% CI:-0.01 to 0.02) increase in $\dot{V}O_2$ and a 0.02 (95% CI: -0.02 to -0.02) multiplied by $\dot{V}_E$ (L) decrease in $\dot{V}O_2$.
- Kg increase in body mass there is a 0.02 mL.Kg.$^{-1}$min^{-1}(95% CI: -0.04-0.01) decrease in $\dot{V}O_2$.
- year increase in age there is a 0.04 mL.Kg.$^{-1}$min^{-1} (95% CI: -0.08; -0.00) decrease in $\dot{V}O_2$.

Simulation (n = 50) of the $\dot{V}_E$ model with 95% confidence intervals is given in *Figure 6.21*.

	REMB	$\dot{V}_E$	Age	Weight
Intercept	4.32***	0.56*	7.17***	5.57***
	(0.17)	(0.25)	(0.90)	(0.67)
$\dot{V}_E$		0.30***		
		(0.00)		
Age			−0.04**	
			(0.01)	
Weight				−0.02·
				(0.01)
AIC	39785.92	23682.97	39779.64	39784.46
BIC	39817.27	23722.16	39818.83	39823.65
Log Likelihood	−19888.96	−11836.48	−19884.82	−19887.23
Num. obs.	18745	18745	18745	18745
Num. sessions	44	44	44	44
Num. patients	19	19	19	19
RE variance: session	0.24	0.12	0.24	0.24
RE variance: patient	0.42	1.15	0.23	0.34
Residual variance	0.48	0.20	0.48	0.48

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, $^{\cdot}p < 0.1$

Table 6.9: $\dot{V}_E$ model. Random effects (patient and session) and univariate associations, $\dot{V}_E$, age and weight. AIC = Akaike's information criterion, BIC = Bayesian information criterion, RE = Random effect, refering to the grouping structure; patient or session.

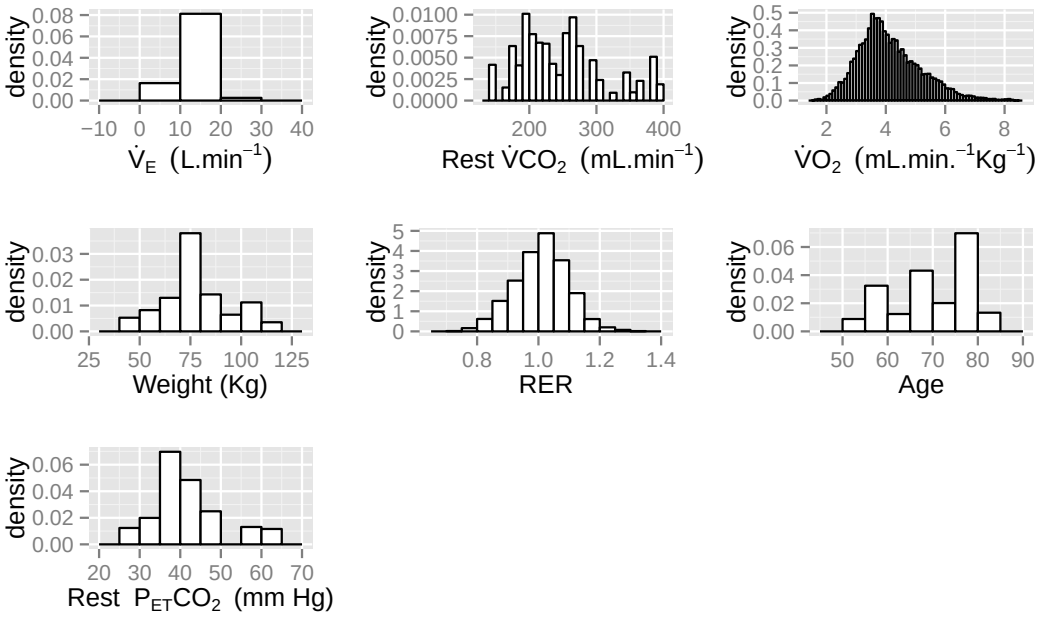


Figure 6.15: $\dot{V}_E$ model. Histograms of dependent and independent variables and RER.

	$\dot{V}_E$	MB3a	MB3b	MB3c	MB3d	MB3e
Intercept	0.56*	0.03	−2.76***	0.57*	0.58*	−2.54***
	(0.25)	(0.66)	(0.70)	(0.25)	(0.25)	(0.65)
$\dot{V}_E$	0.30***	0.30***	0.52***	0.30***	0.30***	0.54***
	(0.00)	(0.00)	(0.01)	(0.00)	(0.00)	(0.01)
Rest $P_{ET}CO_2$		0.01	0.08***			0.07***
		(0.01)	(0.02)			(0.01)
$\dot{V}_E$:Rest $P_{ET}CO_2$			−0.01***			−0.01***
			(0.00)			(0.00)
Rest $\dot{V}CO_2$				−0.23*	−0.09	−0.04
				(0.12)	(0.11)	(0.12)
$\dot{V}_E$:Rest $\dot{V}CO_2$					−0.01***	−0.02***
					(0.00)	(0.00)
AIC	23682.97	23684.24	22651.78	23681.20	23641.23	22502.23
BIC	23722.16	23731.27	22706.65	23728.23	23696.10	22572.78
Log Likelihood	−11836.48	−11836.12	−11318.89	−11834.60	−11813.61	−11242.12
Num. obs.	18745	18745	18745	18745	18745	18745
Num. sessions	44	44	44	44	44	44
Num. patients	19	19	19	19	19	19
RE variance: session	0.12	0.11	0.14	0.10	0.10	0.11
RE variance: patient	1.15	1.12	1.04	1.10	1.11	1.00
Residual variance	0.20	0.20	0.19	0.20	0.20	0.19

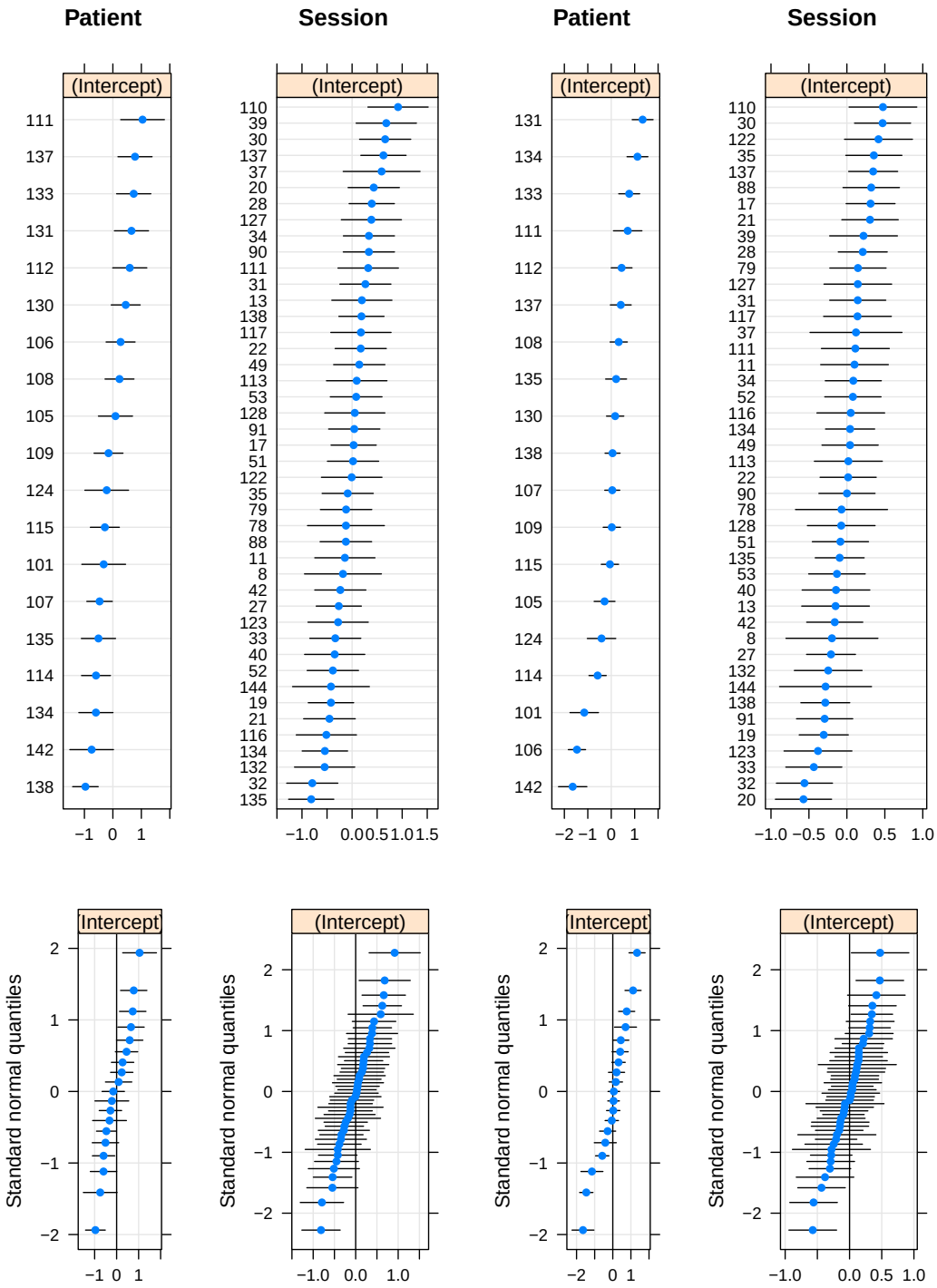
$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 6.10: $\dot{V}_E$ interaction terms. MB3a = $\dot{V}_E$ and Rest $P_{ET}CO_2$ as independent variables, MB3b = $\dot{V}_E$ and Rest $P_{ET}CO_2$ as an interaction term, MB3c = $\dot{V}_E$ and Rest $\dot{V}CO_2$ as independent variables, MB3d = $\dot{V}_E$ and Rest $\dot{V}CO_2$ as an interaction term, MB3e = both $\dot{V}_E$ and Rest $P_{ET}CO_2$ and $\dot{V}_E$ and Rest $\dot{V}CO_2$ as interactions terms. AIC = Akaike's information criterion, BIC = Bayesian information criterion, RE = Random effect, refering to the grouping structure; patient or session.

	MB3e	MB5a	MB5b	MB5c	MB5d
Intercept	-2.54^{***}	-1.21	0.61	1.33	1.43
	(0.65)	(1.05)	(1.51)	(1.52)	(1.63)
$\dot{V}_E$	0.54^{***}	0.54^{***}	0.54^{***}	0.54^{***}	0.54^{***}
	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)
Rest $\dot{V}CO_2$	-0.04	0.05	-0.08	0.01	0.01
	(0.12)	(0.13)	(0.12)	(0.13)	(0.13)
Rest $P_{ET}CO_2$	0.07^{***}	0.08^{***}	0.07^{***}	0.08^{***}	0.08^{***}
	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)
$\dot{V}_E$:Rest $\dot{V}CO_2$	-0.02^{***}	-0.02^{***}	-0.02^{***}	-0.02^{***}	-0.02^{***}
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
$\dot{V}_E$:Rest $P_{ET}CO_2$	-0.01^{***}	-0.01^{***}	-0.01^{***}	-0.01^{***}	-0.01^{***}
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Weight		-0.02		-0.02	-0.02
		(0.01)		(0.01)	(0.01)
Age			-0.05^{*}	-0.04^{*}	-0.04^{*}
			(0.02)	(0.02)	(0.02)
Gender					-0.07
					(0.42)
AIC	22502.23	22501.80	22499.38	22499.41	22501.38
BIC	22572.78	22580.19	22577.77	22585.63	22595.44
Log Likelihood	-11242.12	-11240.90	-11239.69	-11238.70	-11238.69
Num. obs.	18745	18745	18745	18745	18745
Num. sessions	44	44	44	44	44
Num. patients	19	19	19	19	19
RE variance: session	0.11	0.11	0.11	0.11	0.11
RE variance: patient	1.00	0.82	0.76	0.66	0.66
Residual variance	0.19	0.19	0.19	0.19	0.19

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 6.11: $\dot{V}_E$ model. Fixed effects, age, weight. AIC = Akaike's information criterion, BIC = Bayesian information criterion, RE = Random effect, refering to the grouping structure; patient or session.



(a) Random effects only (Patient and session)

(b) Impact of $\dot{V}_E$, weight, age, $\dot{V}CO_2$ and $P_{ET}CO_2$ on the random effects.

Figure 6.16: $\dot{V}_E$ model. Random effects. Caterpillar plots to illustrate the distance, the estimate of the coefficient of the intercept for each patient, or session, lie from the estimated coefficient of the intercept for (a.) the empty model and (b.) the final model.

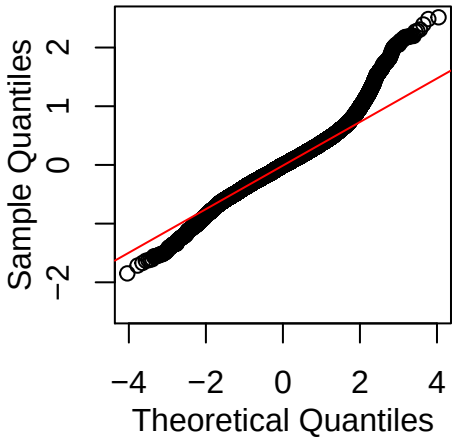


Figure 6.17: $\dot{V}_E$ model. QQnorm. Illustrating the actual residuals plotted against the expected residuals if they were normally distributed. The residuals should lie along the straight line.

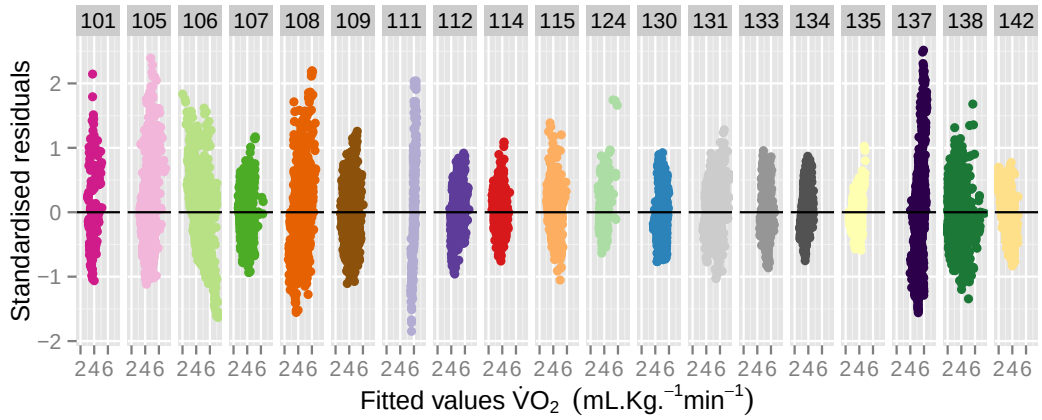


Figure 6.18: $\dot{V}_E$ model. Residuals grouped by patient. Standardised residuals by session. Standardised residuals = residual/SD of all residuals. Thus illustrating how far the estimates lie from the actual values for each patient.

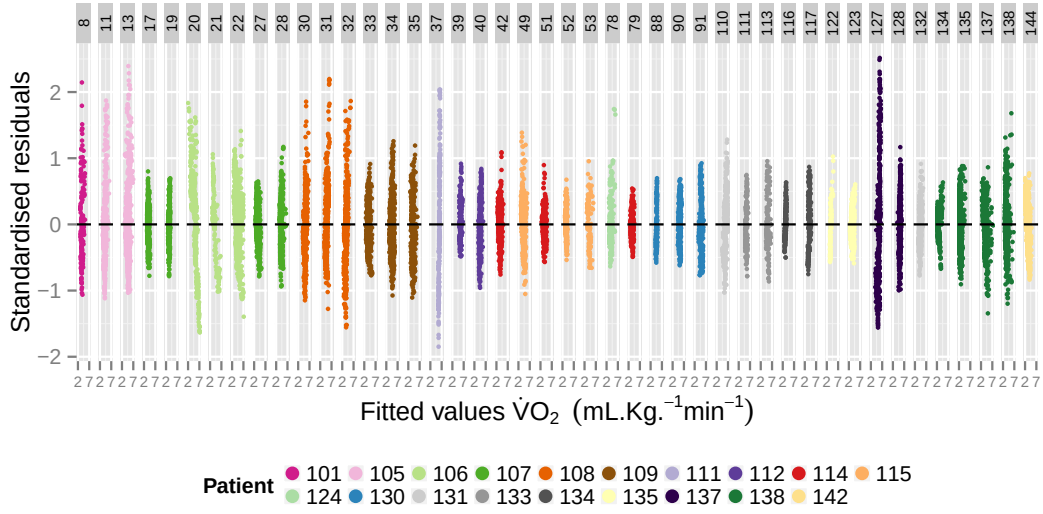


Figure 6.19: $\dot{V}_E$ model. Residuals grouped by session. Residuals grouped by patient. Standardised residuals by session. Standardised residuals = residual/SD of all residuals. Thus illustrating how far the estimates lie from the actual values for each session.

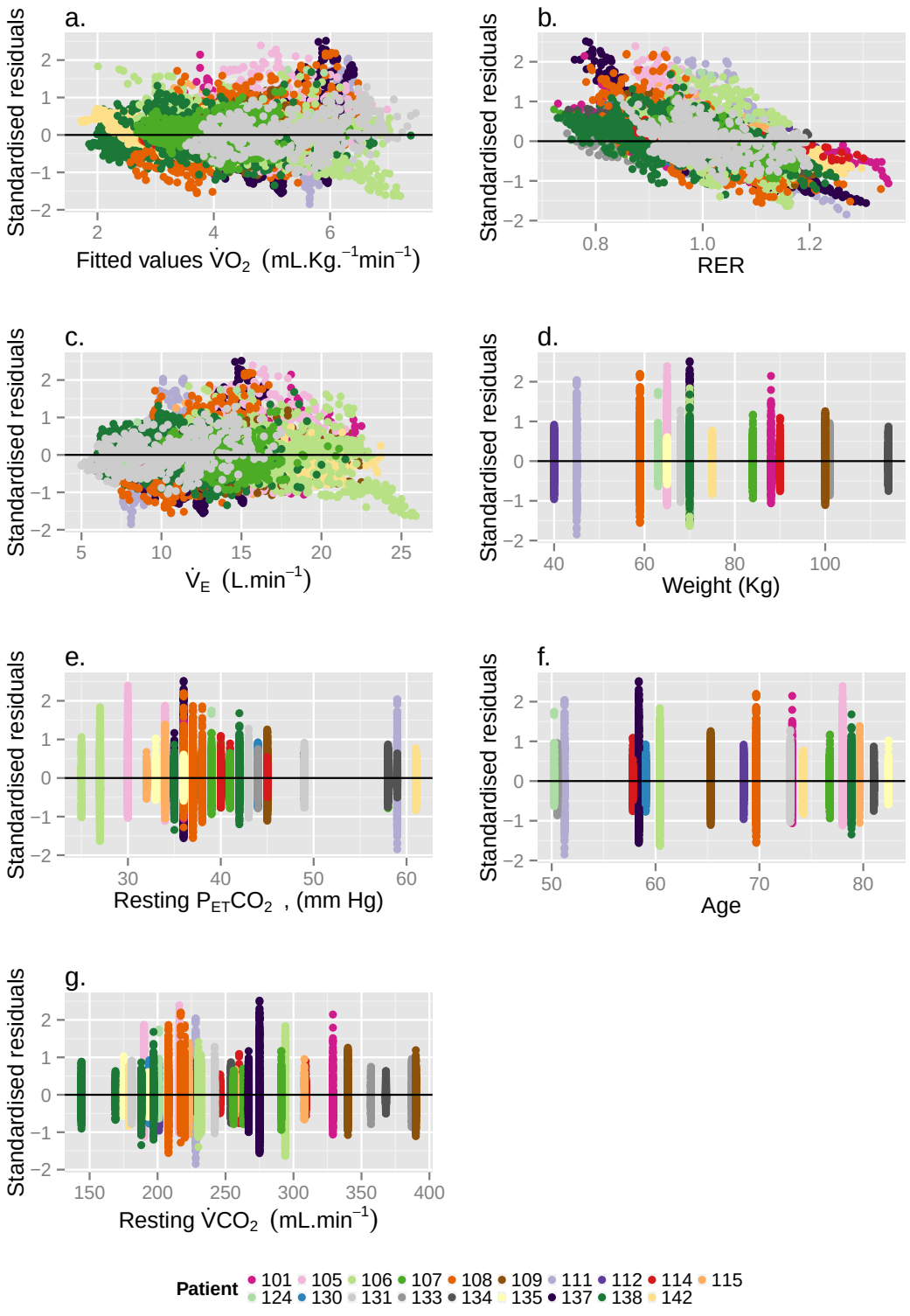


Figure 6.20: $\dot{V}_E$ model. Exploration of standardised residuals by (a). fitted values, (b).RER, and the independent variables (c). $\dot{V}_E$, (d). weight, (e). $P_{ET}CO_2$, (f). age, and (g). $\dot{V}CO_2$. There is no observable bias with the fitted values, weight, $\dot{V}_E$ or age but RER demonstrates bias.

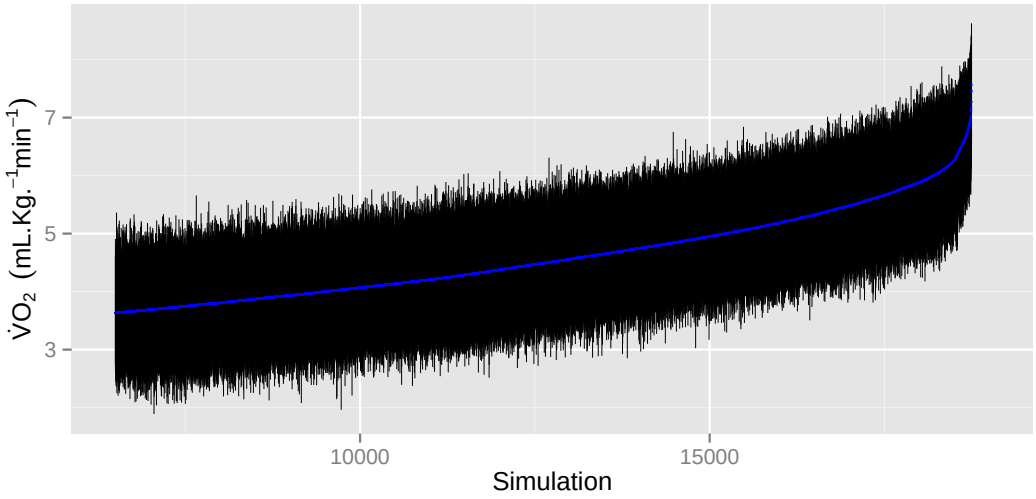


Figure 6.21: $\dot{V}_E$ model. Simulation of values and 95% confidence interval.

6.4.1.2 Categorising $\dot{V}_E$ model into three and four factors.

Reference (actual) and predicted (from the model) $\dot{V}O_2$ mL.Kg.$^{-1}$min^{-1} values were classified as low (<3.5 mL.Kg.$^{-1}$min^{-1}), mid (3.5-4.4 mL.Kg.$^{-1}$min^{-1}) and high (≥4.5 mL.Kg.$^{-1}$min^{-1}) (*Table 6.12*). Confusion matrices were again created (*Figure 6.22*) and multi-group ROC values calculated for the ability of the model to predict the actual $\dot{V}O_2$ values. The same was then done this time creating four categories low (<3.5 mL.Kg.$^{-1}$min^{-1}), mid (3.5-4.24 mL.Kg.$^{-1}$min^{-1}) and high (4.25-4.9 mL.Kg.$^{-1}$min^{-1}) and very high (≥5 mL.Kg.$^{-1}$min^{-1}), (*Table 6.14*).

The stratification of the $\dot{V}_E$ model into three categories (low, mid and high), has positive predictive values (PPV) of 0.83, 0.74 and 0.84 respectively and negative predictive values (NPV) 0.92, 0.83 and 0.94 respectively (*Table 6.13*). The overall multi-class area under the curve is 95.22%. With four categories (low, mid, high and very high), the PPV's were 0.83, 0.74, 0.60 and 0.77 respectively and NPV's 0.92, 0.83, 0.92 and 0.96 respectively (*Table 6.15*). The multi-class area under the curve is 94.83%.

6.5 Summary

Both models to produce relatively similar performance statistics when categorised into three levels. The MROC for the $\dot{V}CO_2$ model 97.45% vs. $\dot{V}_E$ model 95.22% and more usefully into four categories. 96.42% vs. 94.83% respectively.

Class	Category	Range ($mL.Kg.^{-1}min^{-1}$)
1	Low	<3.5
2	Mid	3.5-4.4
3	High	≥4.5

Table 6.12: $\dot{V}_E$ model. Three categories.

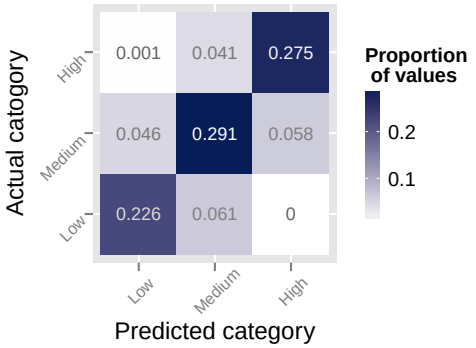


Figure 6.22: $\dot{V}_E$ model. Confusion matrix three categories.

	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value	Prevalence	Detection Rate	Detection Prevalence	Balanced Accuracy
Low	0.79	0.93	0.83	0.92	0.29	0.23	0.27	0.86
Medium	0.74	0.83	0.74	0.83	0.40	0.29	0.39	0.78
High	0.87	0.91	0.82	0.94	0.32	0.27	0.33	0.89

Table 6.13: Performance of $\dot{V}_E$ model with three categories.

Class	Category	Range ($mL.Kg.^{-1}min^{-1}$)
1	Low	<3.5
2	Mid	3.5-4.24
3	High	4.25-4.9
4	Very high	≥5 $mL.Kg.^{-1}min^{-1}$

Table 6.14: $\dot{V}_E$ model. Four categories.

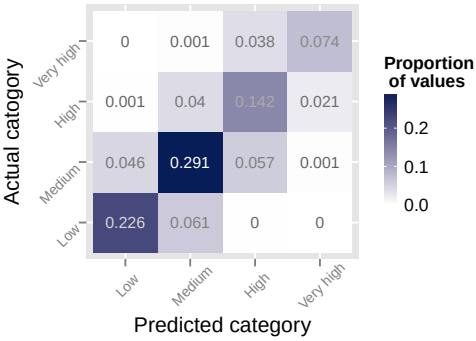


Figure 6.23: $\dot{V}_E$ model. Confusion matrix four categories.

	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value	Prevalence	Detection Rate	Detection Prevalence	Balanced Accuracy
Low	0.79	0.93	0.83	0.92	0.29	0.23	0.27	0.86
Medium	0.74	0.83	0.74	0.83	0.40	0.29	0.39	0.78
High	0.69	0.88	0.60	0.92	0.20	0.14	0.24	0.79
Very high	0.65	0.97	0.77	0.96	0.11	0.07	0.10	0.81

Table 6.15: Performance of $\dot{V}_E$ model with four categories.

6.6 Pilot validation sample

The model will obviously perform well when using its own data. While there is little utility in running a model created from such a small data set, I was curious to see how it would perform. I thus had a preliminary look at the performance of the two models, acknowledging that the original model data set is too small to use for anything other than hypothesis generation. The validation sample is an unusual collection of patients, which may render the sample clinically, if not statistically different from the model sample. This sample comprises of patients for whom there was only one test. Therefore they are either patients at the end of their ICU admission, or patients who had one test and then became too unwell to continue with further rehabilitation, or in whom other tests had unphysiological RER or VE: $\dot{V}O_2$ r^2 values that had to be excluded.

Data from 12 patients with mean RER <1.1 ($\dot{V}CO_2$ model) or a $\dot{V}_E$: $\dot{V}O_2$ $r^2 \geq 0.45$ ($\dot{V}_E$ model) were entered into the previously generated models. M4 = $\dot{V}CO_2$, age and weight. MB5c = $\dot{V}_E$:Rest $\dot{V}CO_2$, $\dot{V}_E$:$P_{ET}CO_2$, age and weight and $\dot{V}O_2$ ($mL.Kg.^{-1}min^{-1}$) predictions calculated. Residuals were plotted and the data re-categorised into three categories. The MROC values and performance statistics were then calculated.

As can be seen from *Figure 6.24* the standardised residuals for the $\dot{V}CO_2$ model validation sample are greater than for the original sample. The $\dot{V}CO_2$ model tends to over estimate the sample values. This is highlighted by the confusion matrix *(Figure 6.28)*, where a greater proportion of actual low level activities are predicted as medium level rather than low level and a greater proportion of medium level as high level. The PPV's for the low and medium activities are less than 0.48 *(Table 6.16)*.

From *Figure 6.26* it can be seen that the standardised residuals in $\dot{V}_E$ model validation sample are considerable, with the bias possibly related to the $\dot{V}_E$ values (*Figure 6.27c*). The model is over-predicting for medium and low $\dot{V}_E$ values (*Figure 6.29*). The NPV's are similar to the $\dot{V}CO_2$ model but both low- and medium-level activity PPV's are less than 0.5 *(Table 6.17)*.

6.6.1 Summary

The residuals of both models are large. This is unsurprising given the limited numbers in the model creation. However, both models warrant further investigation to establish if this is due to a non-linear relationship between the dependent and independent variables. Per-

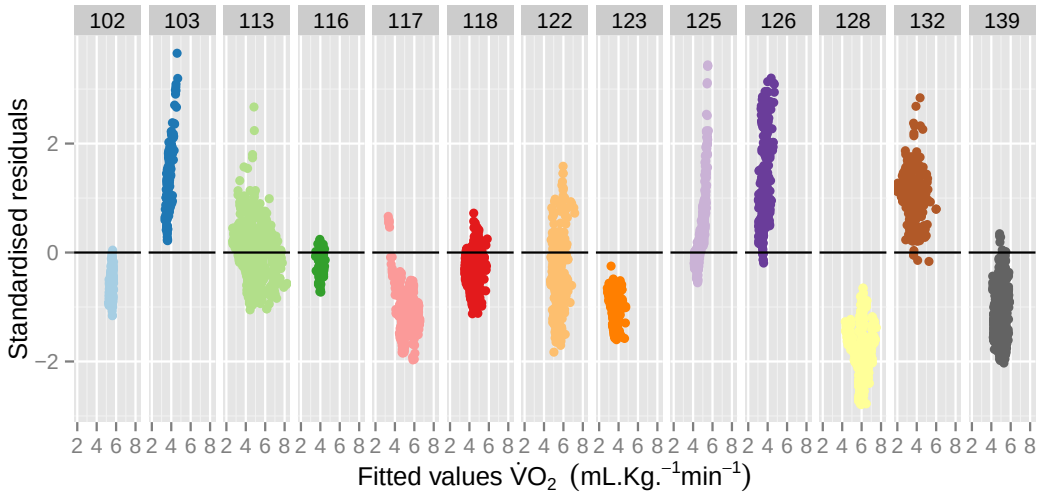


Figure 6.24: $\dot{V}CO_2$ model validation sample, standardised residuals for each patient.

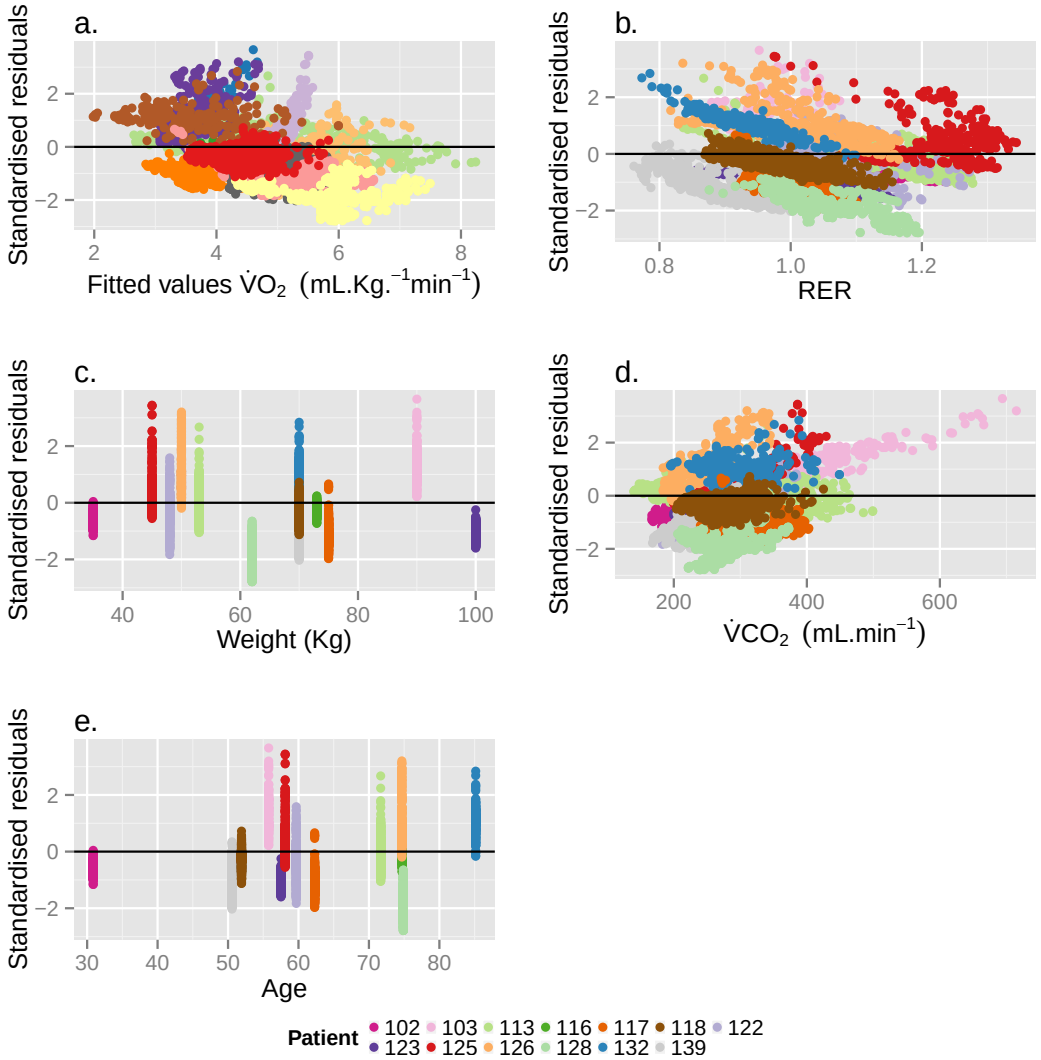


Figure 6.25: Exploration of standardised residuals of $\dot{V}CO_2$ validation model,standardised residuals plotted against (a). Fitted values, (b). RER, and the independent variables (c). weight, (d). $\dot{V}CO_2$ and (e). age.

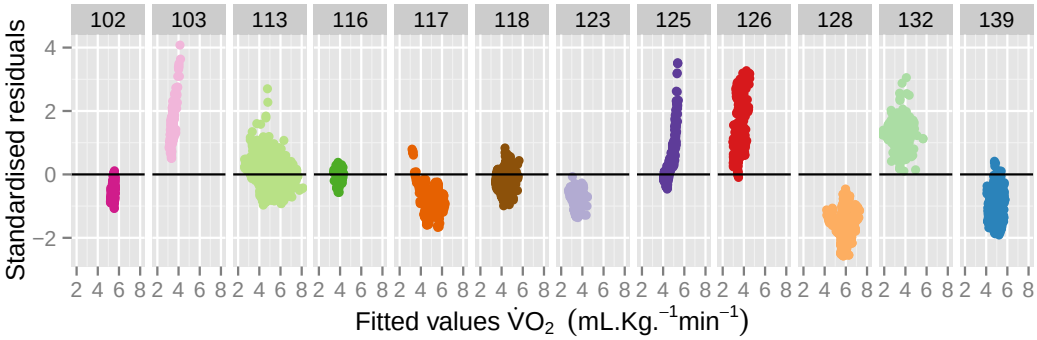


Figure 6.26: $\dot{V}_E$ model validation sample. Residuals by patient.

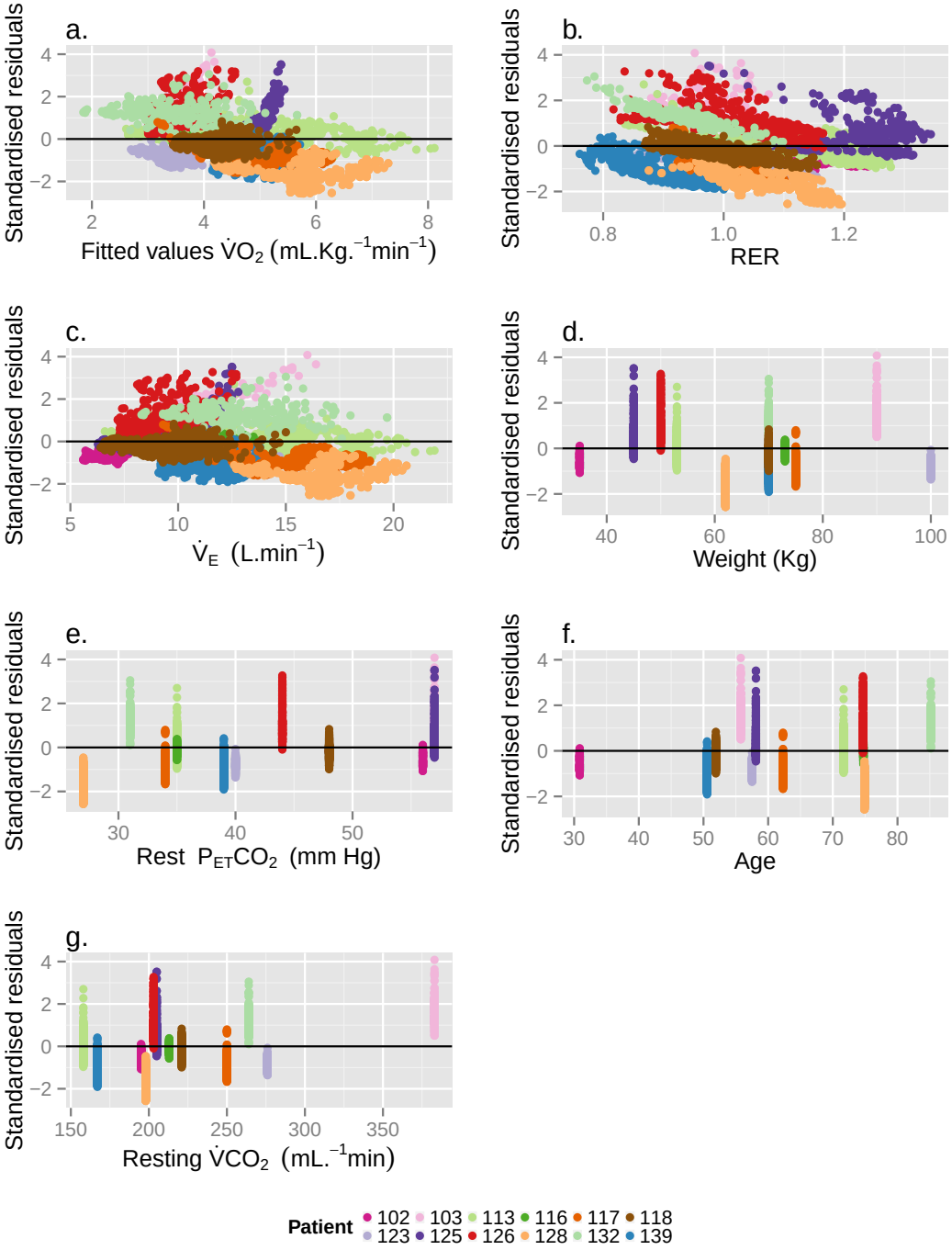


Figure 6.27: $\dot{V}_E$ model validation sample. Standardised residuals by (a). fitted values, (b).RER, and the independent variables (c). $\dot{V}_E$, (d). weight, (e). $P_{ET}CO_2$, (f). age, and (g). $\dot{V}CO_2$

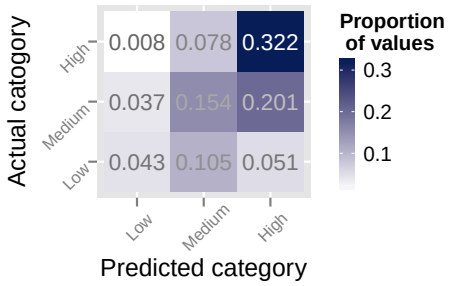


Figure 6.28: Confusion matrix $\dot{V}CO_2$ model in validation sample with three categories.

	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value	Prevalence Rate	Detection Rate	Detection Prevalence	Balanced Accuracy
Low	0.22	0.94	0.49	0.83	0.20	0.04	0.09	0.58
Medium	0.39	0.70	0.46	0.64	0.39	0.15	0.34	0.55
High	0.79	0.57	0.56	0.80	0.41	0.32	0.57	0.68

Table 6.16: Performance of $\dot{V}CO_2$ model in validation sample with three categories.

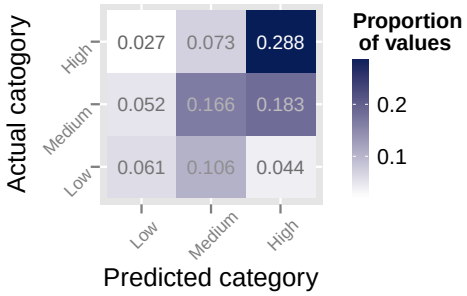


Figure 6.29: $\dot{V}_E$ model in validation sample, confusion matrix with three categories.

	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value	Prevalence Rate	Detection Rate	Detection Prevalence	Balanced Accuracy
Low	0.29	0.90	0.44	0.83	0.21	0.06	0.14	0.59
Medium	0.41	0.70	0.48	0.64	0.40	0.17	0.35	0.56
High	0.74	0.63	0.56	0.79	0.39	0.29	0.51	0.69

Table 6.17: Performance of $\dot{V}_E$ model in validation sample with three categories.

haps a non-linear multilevel model should be used, or some other form of transformation will be required. There were no statistically significant differences between patients in terms of age, gender, weight, duration of mechanical ventilation at enrolment, days to liberations or survival. However, the validation group were recruited slightly later in their ICU admissions and a greater proportion of them survive their admission to ICU. The mean resting $P_{ET}CO_2$, resting $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}CO_2$ and $\dot{V}O_2$ values are all statistically different between the validation and model samples. This will have influenced how the model fits the new data.

Sample	Model		Validation	
n	19		13	
Gender % male	53		46	
% Survived	74		92	
	Mean	SD	Mean	SD
Age	67.80	10.92	62.14	14.14
Weight	74.05	18.53	64.69	18.38
MV prior to enrolment	32.63	21.26	39.69	41.79
Days to liberation	55.95	35.75	55.38	63.34
Worst SOFA	8.58	3.11	9.54	3.28

MV = mechanical ventilation.

Table 6.18: Patient level variables

Sample	Model		Validation	
n	21276		5534	
	Mean	SD	Mean	SD
$\dot{V}CO_2$	308.31	83.77	273.65	63.79
Rest $\dot{V}CO_2$	246.96	65.04	209.84	45.72
Rest $P_{ET}CO_2$	41.23	9.70	40.39	8.85
$\dot{V}_E$	12.79	3.32	11.82	3.31
$\dot{V}O_2$	4.13	1.07	4.32	1.00

Table 6.19: Session level variables.

6.6.2 Conclusion

Proxy values for $\dot{V}O_2$ can be generated from 2 models, one using $\dot{V}CO_2$ and the other using $\dot{V}_E$. Both produce similar performance statistics when $\dot{V}O_2$ is categorised into three levels; low, medium and high intensity. Categorising $\dot{V}O_2$ into four levels; low, medium, high and very high, which probably has greater clinical utility, performs less well. When the models are used to categorise a new set of data, the residuals of both models are large. Nevertheless, given the limited numbers of subjects used for the model creation, both models are worthy of further investigation.

Chapter 7

Summary and future work

Physical function deficits following an ICU admission are the result of a complex interaction of critical illness, its consequent treatments, and bed rest on cardiac, respiratory, neurological and neuromuscular function. Despite the lack of an adequate theoretical framework on which to base rehabilitation strategies, exercise is widely "prescribed" to ameliorate these effects. However, without a method to quantify exercise intensity in patients rehabilitating in the ICU, there is no way of ensuring that some patients are not over-trained while others remain under-trained. Similarly, we do not have a reliable way of establishing if patients enrolled in an interventional limb of a rehabilitation study receive a significantly different exercise load to those randomised to the control group.

The aim of my thesis was to establish a method of quantifying rehabilitation interventions in mechanically ventilated patients with, and recovering from, critical illness (Table 7.1). I have identified two potential methods, both of which require further validation. Breath-by-breath gas exchange analysis is a useful but impractical tool in the ICU setting. While it provides valuable information regarding the patient's oxygen consumption, both at rest for titration of nutritional requirements and during rehabilitation to monitor absolute exercise intensity, the limited number of interpretable tests obtained during rehabilitation precludes its use as a clinical tool.

BBGEA devices have been designed for use in athletes who generate a far higher minute ventilation than patients. Therefore, the previously accepted inherent errors with the technique become magnified when transferred to an ICU patient population. Unfortunately, manufacturers have failed to take this into account when adapting the technology to the critical care setting. For such devices to be useful, industry needs to work with clinicians to create a device that is portable, quick to set up and calibrate, is not influenced by flow-by circuits,

Objective		Comment	Chapter
1. To validate a medical device to measure oxygen consumption in mechanically ventilated patients.		Accomplished	4.5
2. To develop a standardised, reproducible exercise stimulus.	**a.** Establish the feasibility of BBGEA in MV patients during rehabilitation.	Sequential constant load arm ergometry tests identified as a potential way to measure anaerobic threshold.	5.5
	b. Evaluate the feasibility of arm cycle ergometery in MV patients.		5.6
3. To identify a method of quantifying rehabilitation interventions.		Two Methods identified.	6.2
4. To validate the measurement tool.		Partly accomplished. Further work required.	6.5

MV = mechanically ventilated, BBGEA = Breath by breath gas exchange analysis.

Table 7.1: Thesis objectives and outputs.

does not get blocked by sputum, and whose precision remains unaffected at low levels of $\dot{V}O_2$ in the presence of an increased inspired oxygen concentration. However, given that the most frequent source of error was the instability of the inspired oxygen concentration generated by the ventilator, such a device would ideally be integrated into the ventilator itself, in conjunction with improvements in the regulation of the delivered oxygen concentration. While an error of 2-7% is accepted as a reasonable fluctuation in the delivery of oxygen in clinical practice, this is not acceptable for most BBGEA devices. The accuracy of the MGU reported here must be interpreted within the context of the limitations in the accuracy of the reference devices (see Chapter 4).

7.1 Key outputs

Breath-by-breath-gas exchange analysis is a challenging technique during resting metabolic studies, and one that becomes increasingly more challenging when patients begin to exercise. Partly because of an increased cough frequency due to mobilisation of secretions, but also as inspiratory flow rates become more erratic, the instability of the delivered F_iO_2 increases, rendering some of the tests unusable. Therefore, the time-consuming nature of the technique and the proportion of unusable data sets result in a technique that has little day-to-day utility. From a research perspective, documentation of the session, monitoring the running of the MGU device, and blood sampling were infeasible for one person alone. Despite these challenges, it was still possible to identify several factors that are relevant to clinical rehabilitation practice within the ICU.

$\dot{V}O_2$ is not activity dependent. The $\dot{V}O_2$ of rehabilitation activities is not consistent between patients, or indeed within patients when measured over time (see Chapter 5). Patients with lower physical function levels (as measured by the ICU-FSS) utilise less oxygen than those with higher physical function levels. Therefore, one cannot assume that the same rehabilitation activity has the same oxygen cost for each patient. However, given the small numbers of patients this study is based upon, further investigation is warranted. Especially as it raises the question of why patients with lower functional capacity utilise less oxygen. Functional capacity assessments evaluate limitations in activities and therefore takes into account a multitude of both physical and psychological impairments. In the absence of contemporaneous lactate measurements, it is impossible to begin to speculate on the point of limitation in the oxygen consumption chain. Possibilities include decreased gas exchange, reduced cardiac output and oxygen delivery to the exercising muscles, reduced muscle mass, more readily fatigable muscle, and/or a bioenergetics-metabolic failure.

Pressure support. The regression analysis in Chapter 5 highlighted pressure support as a variable that was associated with an increase in the oxygen consumed during a rehabilitation session. How this occurs is difficult to pinpoint given the available data, but it could be due to patients being able to exercise for longer if their breathing is offloaded. Alternatively the rate-limiting step in the ability to consume oxygen is related to lung mechanics and/or cardiac function. This effect could be explored by repeating the same activity at different levels of ventilatory support with concurrent lactate measurements.

Patient efficiency compared to healthy individuals. The decrease in patient efficiency was almost, but not entirely, explained by the length of time to carry out an activity. One hypothesis for the discrepancy could be the selective type I fibre atrophy seen in patients with ICUAW, the bioenergetic consequences of which would be a reduction in $\dot{V}O_2$ for a given workload, similar to that seen in COPD patients. To investigate this, the same activity would ideally be repeated on different days, with comparison to an age- and gender-matched population. Unfortunately, given the nature of rehabilitation in the ICU, i.e. the very low exercise tolerance patients experience, those who can sit do not necessarily want to practice sitting as they want to progress to standing and walking and not waste time and energy repeating an activity they can already perform.

Heart rate. My original conjecture that heart rate would not be a useful indicator of exercise intensity was well founded. None of the heart rate indicators used in my regression analysis had univariate or multivariate associations with $\dot{V}O_2$. A large proportion of the patients enrolled were receiving heart rate-limiting drugs. Indeed, their heart rate responses were similar to

those reported in the free living population receiving such drugs. This reinforces my view that HR indices are not useful in this population.

Heart rate variability. Heart rate variability measurement in the ICU setting is not readily possible given the hardware currently available.

Sample size calculations. Sufficient data have been collected to enable me to make reasonable assumptions regarding sample size calculations for future studies involving $\dot{V}O_2$ measurements during rehabilitation in mechanically ventilated patients.

Rate of percieved exertion. Accurate and repeatable reports of patient RPE were not possible in this particular patient group.

Arm cycle ergometery as a standardised exercise test. Early on, it became apparent to me that incremental arm cycle ergometry was non-feasible in this cohort of patients. However, it may be possible to identify AT through a series of constant load ergometery tests. To generate comparable workloads both between and within patients, a consistent pedal frequency (RPM) needs to be generated on the ergometer. At lower RPMs the work rate increases due to the need to overcome the inertia of the ergometer. This issue is not unique to this study. Ideally, a cycle ergometry device that could be used while the patient remained in bed, had a powered fly-wheel to ensure accurate unloaded pedaling, was accurate at low RPMs, and that could be either arm- or leg-propelled would be used.

Data from the cycle ergometry study provide a means of identifying those patients who would be able to cycle the requisite three minutes. Although this would only capture patients at the more physically able end of the spectrum in the ICU, it could establish the extent of their deconditioning. This would provide a way of measuring exercise capacity that is comparable both between and within patients over time, albeit in a subset of the ICU rehabilitation population. Again, these $\dot{V}O_2$ data would need to be corroborated with lactate data.

$\dot{V}_E$ as an indicator of $\dot{V}O_2$ returning to baseline. The return of $\dot{V}_E$ to baseline is indicative of $\dot{V}O_2$ returning to baseline. This is a very simple and easy way to establish recovery from exercise bouts during rehabilitation.

Estimation of $\dot{V}O_2$ from $\dot{V}_E$ or $\dot{V}CO_2$. The interpretation of the models for $\dot{V}_E$ and $\dot{V}CO_2$ estimation of $\dot{V}O_2$ are limited purely to exploration of the variables that might influence either model. This is due to the limited number of patients that the models are based upon. From the data acquired from this study, a sample size of at least 60 patients would

be required to establish clinical equivalence with 90% power, where equivalence is achieved if a 95% confidence interval for the difference in the actual and predicted values is wholly contained within ± 1 ml.Kg.$^{-1}$min.$^{-1}$ (25% limits, based on 4.5 ml.Kg.$^{-1}$min.$^{-1}$ $\dot{V}O_2$).

7.1.1 Limitations

7.1.1.1 MGU validation study

The validation study was based on a relatively small sample size. The inaccuracy of the reference techniques also needs to be acknowledged. There are multiple potential sources of error in the Douglas bag technique as well as multiple conversion of gas properties. As much as possible was done to minimise the potential errors in the Douglas bag technique using correction factors and pre-validation calibration. Two blood gas analysis machines were used as one broke part way through the study, although calibration equations were performed for both devices.

7.1.1.2 Rehabilitation studies

The sample size recruited was small but probably reflected the ICU rehabilitation population at UCH. A large proportion of the data was not interpretable; is not possible to establish whether this introduced any bias into the results. The high RER values are concerning, but are likely explained by patients hyperventilating in anticipation of their rehabilitation session. The repeatability of the tests within patients was not established. There were insufficient repeated tests over time to establish wether the regression model was influenced by time.

7.1.2 Issues that require further investigation.

1. To what extent is the hyperbolic nature of RER during exercise influencing the non-linear relationship between $\dot{V}O_2$ and $\dot{V}CO_2$?

2. Is it possible to transform the data to linearise this relationship, or is it possible to use a non-linear-mixed-effects model?

3. Is the non-linear relationship between $\dot{V}O_2$ and $\dot{V}CO_2$ and between $\dot{V}O_2$ and $\dot{V}_E$ due in part to patients exercising above their AT?

4. Does the relationship between $\dot{V}O_2$ and $\dot{V}CO_2$ and between $\dot{V}O_2$ and $\dot{V}_E$ change over the course of a patient's admission?

The huge variations in the exercise load of rehabilitation interventions between and within patients highlights the need to establish personalised exercise regimens.

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Appendices

Appendix A

MGU validation

A.1 GESV values for the 13 tests.

Test	bpm	V_T	Flow	Gas	Expected	Actual	% error
1	10	1	20	CO_2	0.3	0.312	-4.00
6	20	0.5	20	CO_2	1.694	1.597	5.73
6	20	0.5	20	O_2	1.708	1.629	4.63
7	10	0.5	40	CO_2	0.3	0.292	2.67
7	10	0.5	40	O_2	0.303	0.29	4.29
8	40	0.5	40	CO_2	2.834	2.674	5.65
8	40	0.5	40	O_2	2.857	2.84	0.60
9	40	0.5	40	CO_2	1.694	1.613	4.78
9	40	0.5	40	O_2	1.708	1.756	-2.81
10	40	0.5	40	CO_2	2.834	2.472	12.77
10	40	0.5	40	O_2	2.857	2.669	6.58
11	40	0.5	40	CO_2	1.69	1.642	2.84
11	40	0.5	40	O_2	1.715	1.774	-3.44
1	10	1	20	O_2	0.303	0.282	6.93
3	10	1	20	CO_2	0.299	0.326	-9.03
3	10	1	20	O_2	0.304	0.331	-8.88
2	20	1.5	60	CO_2	1.694	1.684	0.59
2	20	1.5	60	O_2	1.708	1.559	8.72
4	20	1.5	60	CO_2	1.689	1.474	12.73
4	20	1.5	60	O_2	1.713	1.573	8.17
5	40	1.5	120	CO_2	2.825	2.54	10.09

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Test	bpm	VT	Flow	Gas	Expected	Actual	% error
5	40	1.5	120	O_2	2.867	2.816	1.78
12	40	1	80	CO_2	1.689	1.554	7.99
12	40	1	80	O_2	1.713	1.589	7.24
13	40	1	80	CO_2	2.825	2.558	9.45
13	40	1	80	O_2	2.867	2.774	3.24

A.2 Deltatrac II flow and RQ calibration $\dot{V}CO_2$ values.

	Flow setting (L.min^{-1})									RQ
Min	41.5	32.8	30.7	32.7	36.9	40.1	30.5	33.1	36.3	
1	612	386	398	137	405	385	384	77	83	
2	549	399	380	385	394	423	376	87	102	
3	524	377	354	360	358	421	357	85	98	
4	524	382	340	335	358	412	334	91	104	
5	486	380	317	295	366	395	321	100	109	
6	460	358	325	314	352	382	316	103	108	
7	450	413	308	299	353	369	320	103	108	
8	415	362	330	312	343	400	313	104	104	
9	400	340	288	322	352	390	310	103	98	
10	400	342	301	313	237	367	295	102	96	
11	10	340	248	312		376	141	98	92	
12						380	60	96	87	
13						317		92	83	
14								89	80	
15								84	77	
16								82	72	
17								78	68	
18								74	66	
19								71	63	
20								67	62	
21								62	59	
22								60	57	
23								57	56	
24								57	56	
25								51	56	
26								50	54	
27								50	51	
28								49	52	
29								46	50	
30								48	52	
31								46	53	
32								45	50	

Continued on the next page...

	Flow setting (L.min^{-1})									RQ
Min	41.5	32.8	30.7	32.7	36.9	40.1	30.5	33.1	36.3	
33								45	50	0.66
34								45	48	0.66
35								30	48	0.67
36								42	48	0.66
37								42	48	0.66
38								42	47	0.65
39								42	48	0.68
40								39	47	0.66
41								40	46	0.66
42								39	46	0.66
43								39	48	0.63
44								40	45	0.66
45								25	47	0.66
46								39	45	0.66
47								40	46	0.66
48								38	46	0.66
49								38	45	0.66
50								37	45	0.65
51								38	44	0.66
52								38	4	0.66
53								38	44	0.66
54								36	43	0.65
55								38	45	0.66
56								37	44	0.66
57								38	43	0.66
58								36	42	0.75
59								38	42	0.68
60								37	43	0.71
61									41	0.72
Sum	4830	4079	3589	3384	3518	5017	3527	3483	3684	
Correction	0.79	0.94	1.06	1.13	1.09	0.76	1.08	1.1	1.04	
New flow	32.8	30.7	32.7	36.9	40.1	30.5	33.1	36.3	37.6	0.67

A.3 Douglas bag calculations

A.3.1 $\dot{V}O_2$,$\dot{V}CO_2$, and REE calculations NOT accounting for flow-by.

Abbreviation	Explanation
T_{ET}/T_{TOT}	Ratio of expiratory time to total breath-cycle time
V_E	Volume of gas collected in PVC collection bag
$O_{2(E)}$	Expired oxygen
V_I	Volume inspired
pH_2O	Water vapour pressure
F_IO_2	Inspired oxygen concentration
pH_20	partial pressure of water
ST	Standard temperature
BT	Body temperature
AP	Atmospheric pressure
SP	Standard pressure

$$\dot{V}O_{2\ (ATPS)} = (\dot{V}_I * F_IO_2) - (\dot{V}_E * F_EO_2) \tag{A.1}$$

$Where$

$$V_I = \dot{V}_E * \left(\frac{1 - F_{db}O_2 - F_{db}CO_2}{1 - F_iO_2}\right) \begin{cases} where \\ \dot{V}_E = \dot{V}_{db} \\ F_ECO_2 = F_{db}CO_2 \\ F_EO_2 = F_{db}O_2 \end{cases}$$

$Therefore$

$$\dot{V}O_2 = \left(\dot{V}_{db} * \left(\frac{1 - F_{db}O_2 - F_{db}CO_2}{1 - F_iO_2}\right) * F_IO_2\right) - \left(\dot{V}_{db} * F_{db}O_2\right) \tag{A.2}$$

$$\dot{V}CO_{2\ (ATPS)} = \dot{V}_{db} * F_{db}CO_2 \tag{A.3}$$

Conversion of ATPS to STDP (A.4)

$$\dot{V}_{E\ (STPD)} = \dot{V}_{E\ (ATPS)} * \frac{ST}{ST + BT} * \frac{AP - Inspiratory\ pH_20\ 100\ \%RH}{SP}$$

$$REE = 1.44 * \left(3.9 * \dot{V}O_2 + 1.1 * \dot{V}CO_2\right) \left\{ \ Weir\ equation \right. \tag{A.5}$$

A.3.2 $\dot{V}O_2$,$\dot{V}CO_2$, and REE calculations accounting for flow-by.

$$\dot{V}O_{2\ (ATPS)} = (\dot{V}_I * F_IO_2) - (\dot{V}_E * F_EO_2) \tag{A.6}$$

$$\dot{V}_I = \dot{V}_E \cdot \frac{(1 - F_ECO_2 - F_EO_2)}{1 - F_iO_2} \begin{cases} Where \\ \dot{V}_E = \dot{V}_{db} - \dot{V}_{fb} \\ F_EO_2 = \frac{(\dot{V}_{db} * F_{db}O_2) - (\dot{V}_{fb} * F_IO_2)}{\dot{V}_E} \\ or \\ F_EO_2 = \frac{(\dot{V}_{db} * F_{db}O_2) - (\dot{V}_{fb} * F_IO_2)}{\dot{V}_{db} - \dot{V}_{fb}} \\ F_ECO_2 = \frac{(\dot{V}_{db} * F_{db}CO_2)}{\dot{V}_E} \\ F_ECO_2 = \frac{(\dot{V}_{db} * F_{db}CO_2)}{\dot{V}_{db} - \dot{V}_{fb}} \end{cases}$$

Substituting

$$\dot{V}_I = (\dot{V}_{db} - \dot{V}_{fb}) * \frac{\left(1 - \left(\frac{(\dot{V}_{db} * F_{db}O_2) - (\dot{V}_{fb} * F_IO_2)}{\dot{V}_{db} - \dot{V}_{fb}}\right) - \left(\frac{(\dot{V}_{db} * F_{db}CO_2)}{\dot{V}_{db} - \dot{V}_{fb}}\right)\right)}{1 - F_IO_2} \tag{A.7}$$

Therefore

$$\dot{V}O_2\ (ATPS) = \tag{A.8}$$

$$\left((\dot{V}_{db} - \dot{V}_{fb}) * \frac{\left(1 - \left(\frac{(\dot{V}_{db} * F_{db}O_2) - (\dot{V}_{fb} * F_IO_2)}{\dot{V}_{db} - \dot{V}_{fb}}\right) - \left(\frac{(\dot{V}_{db} * F_{db}CO_2)}{\dot{V}_{db} - \dot{V}_{fb}}\right)\right)}{1 - F_IO_2} * F_IO_2\right) -$$

$$\left((\dot{V}_{db} - \dot{V}_{fb}) * \frac{(\dot{V}_{db} * F_{db}O_2) - (\dot{V}_{fb} * F_IO_2)}{\dot{V}_{db} - \dot{V}_{fb}}\right)$$

$$\dot{V}CO_{2\ (ATPS)} = \dot{V}_E * F_ECO_2 \begin{cases} Where \\ F_ECO_2 = \frac{\dot{V}_{db} * F_{db}CO_2}{\dot{V}_{db} - \dot{V}_{fb}} \end{cases}$$

Conversion of ATPS to STDP (A.9)

$$\dot{V}_{E\ (STPD)} = \dot{V}_{E\ (ATPS)} * \frac{ST}{ST + BT} * \frac{AP - Inspiratory\ pH_20\ 100\ \%RH}{SP} \tag{A.10}$$

$$REE = 1.44 * \left(3.9 * \dot{V}O_2 + 1.1 * \dot{V}CO_2\right) \left\{ \ Weir\ equation \right. \tag{A.11}$$

A.3.3 Douglas bag calculations explanation.

A	Flow-by gas volume 2 L.min^{-1} of the patients F_iO_2 is added for the duration of expiration	$T_{ET}/T_{TOT} * 2$
B	Correction of $\dot{V}_E$ for flow-by gas volume	$V_E - \mathbf{A}$
C	Conversion of partial pressure of O_2 (Kpa) to % accounting for the 30 %RH (HME) and 100% RH (Fisher Paykel) of the sample	$\frac{F_EO_2}{Ambientpressure - pH_2O} * 100$
D	Calibration factor for O_2 electrode of gas machine	y = 1.0403x + 0.6966 (ABL725) y = 1.0346x + 0.9634 (ABL 835)
E	Correction for flow-by (O_2)	$\frac{(\mathbf{D} * V_E) - (A * F_IO_2)}{\mathbf{B}}$
F	Conversion of gas meter CO_2 Kpa to % accounting for 30% RH (HME) and 100% RH (Fisher Paykel) of the sample.	$\frac{F_ECO_2}{Ambientpressure - pH_2O} * 100$
G	Calibration factor for CO_2 electrode of gas machine.	y = 1.1264x - 0.107 (ABL725) y = 1.1205x - 0.1584 (ABL835)
H	Correction for flow-by (CO_2)	$\frac{(\mathbf{G} * V_E)}{\mathbf{B}}$
I	Calculation of $\dot{V}_I$ (ATPS) from $\dot{V}_E$ (ATPS) (**B**)	$\dot{V}_E$ (ATPS)$* \frac{(1 - F_EO_2 - F_ECO_2)}{1 - F_IO_2}$ Or $\mathbf{B} * \frac{(1 - \mathbf{E} - \mathbf{H})}{(1 - F_IO_2)}$
J	Conversion of $\dot{V}_{I\,(ATPS)}$(**I**) to $\dot{V}_{I\,(STPD)}$	$\dot{V}_{I\,(ATPS)} * \frac{ST}{ST+BT} * \frac{AP - Inspiratory\ pH_20\ 100\ \%RH}{SP}$
K	Conversion of $\dot{V}_{E\,(ATPS)}$ to $\dot{V}_{E\,(STPD)}$ (Oxygen consumption only), where $\dot{V}_{E\,(ATPS)}$	$\dot{V}_{E\,(ATPS)} * \frac{ST}{ST+BT} * \frac{AP - Inspiratory\ pH_20\ 100\ \%RH}{SP}$
L	Conversion of $\dot{V}_{E\,(ATPS)}$ (**B**) to $\dot{V}_{E\,(STPD)}$ (CO_2 only) where $\dot{V}_{E\,(ATPS)} = \dot{V}_E$ uncorrected for flow-by (**X**)	$\dot{V}_{E\,(ATPS)} * \frac{ST}{ST+BT} * \frac{AP - Inspiratory\ pH_20\ 100\ \%RH}{SP}$
M		$VO_2 = ((\mathbf{J} * F_iO_2) - (\mathbf{K} * \mathbf{E})) * 1000$
N		$VCO_2 = (\mathbf{L} * \mathbf{G}) * 1000$
O	RQ	$\frac{VCO_2}{VO_2}$
P	REE	Weir equation $1.44 * \left(3.9 * \dot{V}O_2 + 1.1 * \dot{V}CO_2\right)$

A.4 Example Douglas bag calculation sheet.

ID	72B	Ambient Pressure mmHg	748.872	Ambient Pressure kPa	99.6	O_2 correction	y = 1.0346x + 0.9634	1.0346	0.9364
Date	7.01.11	pH_2O in kPa at Ambient Temp	2.5	Inspiratory Temp Celcius	37	CO_2 correction	y = 1.1205x - 0.1584	1.1205	0.1584
Ambient Temp Celcius	21	Inspiratory pH_2O RH 100% mmHg	47.2						

Bag	Volume Collected ATPS (L)	TE/TTOT	Sample duration (sec)	O_2 I	O_2 E Kpa	CO_2 E Kpa	sample volume	(X) $V_E$atps (l/min)
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)
1	46.1	0.68	309	0.3	25	2.21	0.2	8.99
2	42.8	0.69	306	0.3	24.7	2.11	0.2	8.431
3	46.2	0.68	304	0.3	25	2.22	0.2	9.158

Bag	FB Volume ATPSl/min	Corrected VEatps (l/min)	O_2 (%)	O_2 calibration for GM (Fraction)	O_2 Corr for FB (Fraction)	CO_2 (%)	CO_2 calibration for GM (Fraction)	CO_2 corr FB (Fraction)
	(I)	(J)	(K)	(L)	(M)	(N)	(O)	(P)
1	1.36	7.63	25.75	0.276	0.271	2.276	0.024	0.028
2	1.38	7.051	25.441	0.273	0.267	2.173	0.023	0.027
3	1.36	7.798	25.75	0.276	0.272	2.287	0.024	0.028

Bag	V_IATPS (l/min)	V_I stpd (l/min)	V_E STPD O2 (l/min)	V_E STPD CO2 (l/min)	VO_2 (ml/min) STPD	VCO_2 (ml/min) STPD	RQ	REE
1	7.63	6.21	6.2	7.31	178.09	174.86	0.98	1277
2	7.11	5.78	5.73	6.86	201.72	156.08	0.77	1380
3	7.8	6.34	6.34	7.45	181.05	178.98	0.99	1300
				Mean	186.953	169.97	0.91	

A.5 Bland Altman percentage difference plots

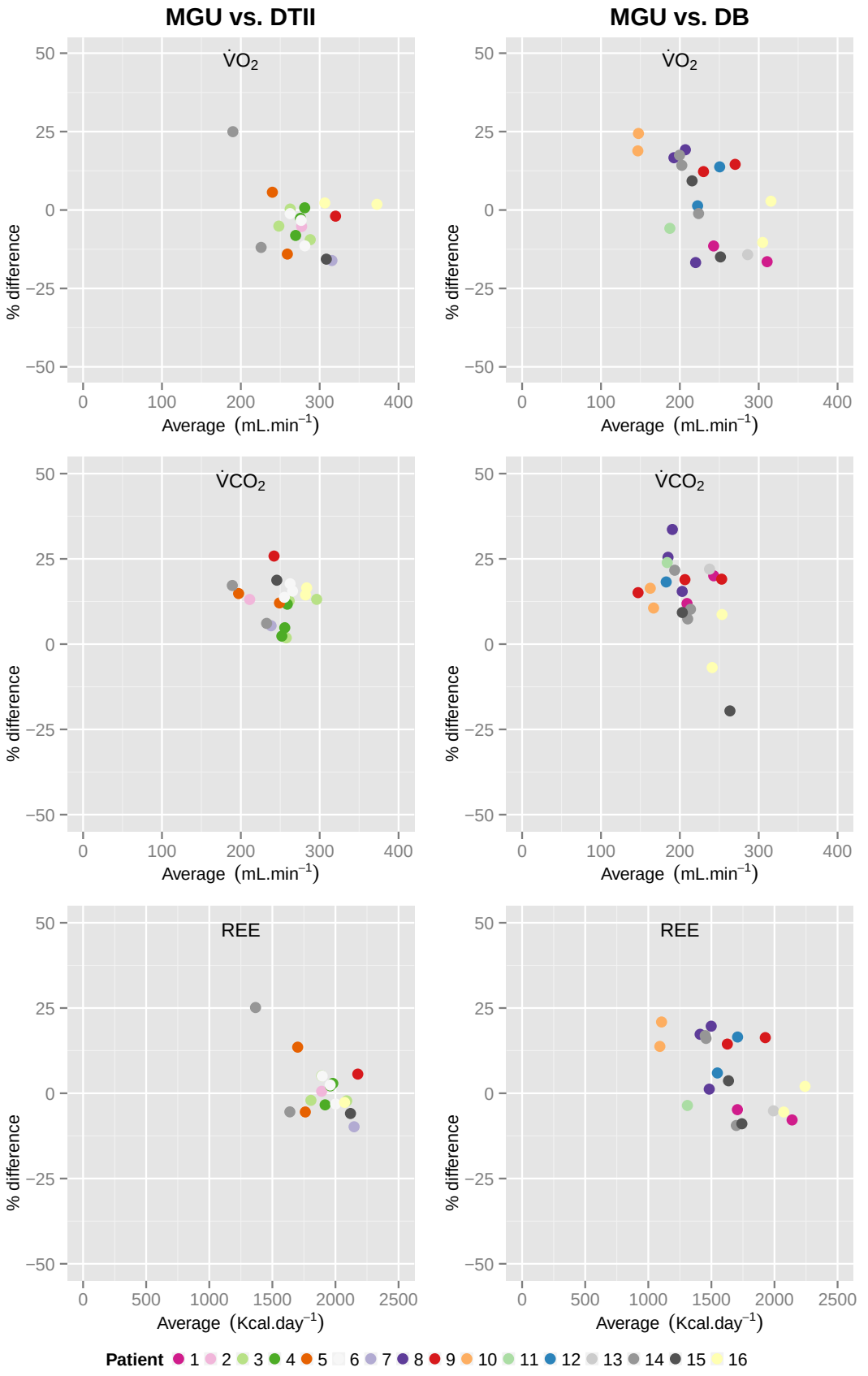


Figure A.1: Bland Altman analysis plotted as percentage difference. $\dot{V}O_2$, $\dot{V}CO_2$ and REE.

Appendix B

Quantifying exercise intensity in ICU, protocol information

B.1 Screening patients prior to exercise

1. No drugs supporting blood pressure e.g., epinephrine, norepinephrine.
2. Resting HR <110 but >60 bpm.
3. No hypertension at rest (>180 mm Hg systolic or >120 mm Hg diastolic).
4. No syncope, multi-focal premature ventricular contractions, or high-degree atrio-ventricular block.
5. F_iO_2 <0.6
6. P:F ratio >20
7. Hb >70 g/L

B.2 Indications for termination of rehabilitation sessions.

1. Chest pain suggestive of ischaemia.
2. Ischaemic ECG changes
3. Complex ectopy, second or third degree heart block
4. Fall in systolic pressure >20 mmHg from the highest value during the test
5. Hypertension (>200 mmHg systolic; >120 mmHg diastolic)
6. Severe desaturation: S_aO_2 <85%
7. Sudden pallor
8. Loss of coordination
9. Mental confusion
10. Dizziness or faintness

B.3 ICU Functional Status Score

Rolling, Supine to sit, Sitting, Sit to stand, and Ambulation are scored as *Table B.1.*

Score	Description
0	= unable to perform
1	= total assistance (subject 0%)
2	= maximum assistance (subject 25% +)
3	= moderate assistance (subject 50% +)
4	= minimum assistance (subject 75% +)
5	= supervision
6	= modified independence (requires assistive device)
7	= complete independence

Table B.1: ICU-FSS

B.4 General practice physical activity questionaire

General Practice Physical Activity Questionnaire

Date……

Name……..

1. Please tell us the type and amount of physical activity involved in your work.

		Please mark one box only
a	I am not in employment (e.g. retired, retired for health reasons, unemployed, full-time carer etc.)	
b	I spend most of my time at work sitting (such as in an office)	
c	I spend most of my time at work standing or walking. However, my work does not require much intense physical effort (e.g. shop assistant, hairdresser, security guard, childminder, etc.)	
d	My work involves definite physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter, cleaner, hospital nurse, gardener, postal delivery workers etc.)	
e	My work involves vigorous physical activity including handling of very heavy objects (e.g. scaffolder, construction worker, refuse collector, etc.)	

2. During the *last week*, how many hours did you spend on each of the following activities? *Please answer whether you are in employment or not*

Please mark one box only on each row

		None	**Some but less than 1 hour**	**1 hour but less than 3 hours**	**3 hours or more**
a	Physical exercise such as swimming, jogging, aerobics, football, tennis, gym workout etc.				
b	Cycling, including cycling to work and during leisure time				
c	Walking, including walking to work, shopping, for pleasure etc.				
d	Housework/Childcare				
e	Gardening/DIY				

3. How would you describe your usual walking pace? Please mark one box only.

Slow pace (i.e. less than 3 mph)		Steady average pace	
Brisk pace		Fast pace (i.e. over 4mph)	

B.5 Borg RPE scale

University College London Hospitals NHS
NHS Foundation Trust

Intensive Care Unit
3rd floor
University College Hospital
235 Euston Road
London
NW1 2BU
Telephone: 020 7380 9012
Fax: 020 7691 5732

Borg Rate of Perceived Exertion

6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
19	Very very hard
20	

B.6 Monarch arm ergometer calibration.

Dynamic calibration

MONARK EXERCISE AB

Model: 839 E
Date: 2011-06-21
Serial number: Prod.bike
Executed by: AKV

Cycle constant:	1.05
Speed:	33 rpm
Min error ±	5 W
Max error ±	5 %

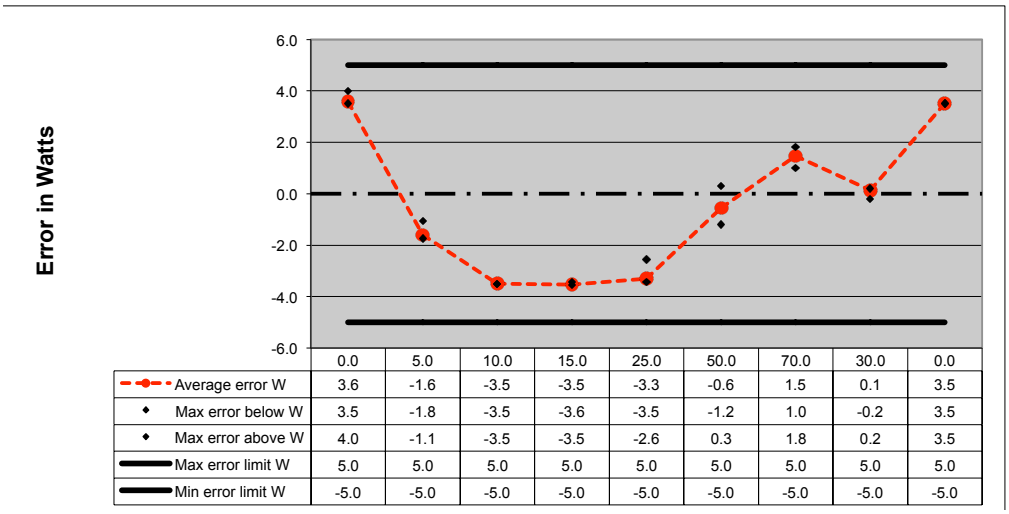
Comments

Production bike, no serial number.
Stable rpm-value is obtained at 33 rpm.
Stable Watt-value is obtained at 31 rpm

Force unit	Read values from calibrator (up to ten runs) W									
W	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
0	4	3.5	3.5	3.5	3.5	3.5				
5	4.2	3.7	3.5	3.5	3.5	3.5				
10	7	7	7	7	7	7				
15	12.3	12.2	12.2	12.2	12.2	12.2				
25	23.7	22.8	22.8	22.8	22.8	22.8				
50	51.9	51.9	51.3	51.9	51.9	52.8				
70	74.5	75.2	75.3	74.6	74.9	75.3				
30	31.7	31.3	31.7	31.7	31.7	31.7				
0	3.5	3.5	3.5	3.5	3.5	3.5				

Calibrator is calibrated daily before use

Calculated values				Values from table above						
W set on bike	Aimed calibrator value W	Max error limit W	Min error limit W	Average W	Average error W	Lowest reading W	Max error below W	Highest reading W	Max error above W	Average error %
0.0	0.0	5.0	-5.0	**4**	3.6	**3.5**	3.5	**4**	4.0	<Wmin
5.0	5.3	5.0	-5.0	**4**	-1.6	**3.5**	-1.8	**4.2**	-1.1	<Wmin
10.0	10.5	5.0	-5.0	**7**	-3.5	**7**	-3.5	**7**	-3.5	<Wmin
15.0	15.8	5.0	-5.0	**12**	-3.5	**12.2**	-3.6	**12.3**	-3.5	<Wmin
25.0	26.3	5.0	-5.0	**23**	-3.3	**22.8**	-3.5	**23.7**	-2.6	<Wmin
50.0	52.5	5.0	-5.0	**52**	-0.6	**51.3**	-1.2	**52.8**	0.3	<Wmin
70.0	73.5	5.0	-5.0	**75**	1.5	**74.5**	1.0	**75.3**	1.8	<Wmin
30.0	31.5	5.0	-5.0	**32**	0.1	**31.3**	-0.2	**31.7**	0.2	<Wmin
0.0	0.0	5.0	-5.0	**4**	3.5	**3.5**	3.5	**3.5**	3.5	<Wmin



	0.0	5.0	10.0	15.0	25.0	50.0	70.0	30.0	0.0
Average error W	3.6	-1.6	-3.5	-3.5	-3.3	-0.6	1.5	0.1	3.5
Max error below W	3.5	-1.8	-3.5	-3.6	-3.5	-1.2	1.0	-0.2	3.5
Max error above W	4.0	-1.1	-3.5	-3.5	-2.6	0.3	1.8	0.2	3.5
Max error limit W	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Min error limit W	-5.0	-5.0	-5.0	-5.0	-5.0	-5.0	-5.0	-5.0	-5.0

B.7 Pre- and post-exercise questionnaire

University College London Hospitals NHS
NHS Foundation Trust

Intensive Care Unit
3rd floor
University College Hospital
235 Euston Road
London
NW1 2BU
Telephone: 020 7380 9012
Fax: 020 7691 5732

Pre and Post Exercise Questionnaire

Quantification of Exercise Intensity in Patients Recovering from Critical Illness

Study Investigator: Claire Black

University College London Hospitals NHS
NHS Foundation Trust

Pre-exercise questionnaire

Patient ID Date Time

Some but not all patients experience pain during their ICU stay. Please rate your current level of pain

0 1 2 3 4 5 6 7 8 9 10
No pain Worst pain

Some but not all patients experience tiredness during their ICU stay. Please rate your fatigue (weariness and tiredness) right NOW

0 1 2 3 4 5 6 7 8 9 10
No fatigue As bad as you can imagine

Some but not all patients experience breathlessness during their ICU stay. Please rate your breathlessness right NOW

0 1 2 3 4 5 6 7 8 9 10
No fatigue As bad as you can imagine

Below is a list of words that describe the way people sometimes feel in hospital. Please circle ONE answer for each question that is nearest to the way you are feeling at the moment

Sad Not at all | A little | Moderately | Quite a bit | Extremely

Discouraged Not at all | A little | Moderately | Quite a bit | Extremely

Anxious Not at all | A little | Moderately | Quite a bit | Extremely

Resentful Not at all | A little | Moderately | Quite a bit | Extremely

Angry Not at all | A little | Moderately | Quite a bit | Extremely

Active Not at all | A little | Moderately | Quite a bit | Extremely

Energetic Not at all | A little | Moderately | Quite a bit | Extremely

University College London Hospitals NHS
NHS Foundation Trust

Post-exercise questionnaire

Please rate your current level of pain

0 1 2 3 4 5 6 7 8 9 10
No pain Worst pain

Please rate your fatigue (weariness and tiredness) right NOW

0 1 2 3 4 5 6 7 8 9 10
No fatigue As bad as you can imagine

How do you feel physically now you have finished exercising?

How do you feel emotionally now you have finished exercising?

What did you like most and least about the exercise?

B.8 PASW filtering and averaging

B.8.1 PASW script for data averaging

	Command	Explanation
1	Data exported from Breeze Suite to excel and then imported to PASW 20.	
2	DATASET ACTIVATE $DataSet.	All data used.
3	USE ALL.	
4	*Decimal time.	Time transformed from fraction of 24 hours to decimal minutes.
5	COMPUTE Time_2=Time*24.	
6	EXECUTE.	
7	* A. Chart Builder.	Graphs of VT, VE, VO2, RQ and F_IO_2 created.
8	GGRAPH	Upper and lower limits set for each parameter. Figure B.1.
9	/GRAPHDATASET NAME="graphdataset" VARIABLES=Time_2 VtBTPS MISSING=LISTWISE REPORTMISSING=NO	
10	/GRAPHSPEC SOURCE=INLINE.	
11	BEGIN GPL	
12	SOURCE: s=userSource(id("graphdataset"))	
13	DATA: Time_2=col(source(s), name("Time_2"))	
14	DATA: VtBTPS=col(source(s), name("VtBTPS"))	
15	GUIDE: axis(dim(1), label("Time_2"))	
16	GUIDE: axis(dim(2), label("Vt BTPS"))	
17	ELEMENT: line(position(Time_2*VtBTPS), missing.wings())	
18	END GPL.	
19		
20	* Chart Builder.	
21	GGRAPH	

Continued on the next page...

	Command	Explanation
22	/GRAPHDATASET NAME="graphdataset" VARIABLES=Time_2 $F_IO_2$dry MISSING=LISTWISE REPORTMISSING=NO	
23	/GRAPHSPEC SOURCE=INLINE.	
24	BEGIN GPL	
25	SOURCE: s=userSource(id("graphdataset"))	
26	DATA: Time_2=col(source(s), name("Time_2"))	
27	DATA: $F_IO_2$dry=col(source(s), name("$F_IO_2$dry"))	
28	GUIDE: axis(dim(1), label("Time_2"))	
29	GUIDE: axis(dim(2), label("F_IO_2 (dry)"))	
30	ELEMENT: line(position(Time_2*$F_IO_2$dry), missing.wings())	
31	END GPL.	
32	* Chart Builder.	
33	GGRAPH	
34	/GRAPHDATASET NAME="graphdataset" VARIABLES=Time_2 VO2 MISSING=LISTWISE REPORTMISSING=NO	
35	/GRAPHSPEC SOURCE=INLINE.	
36	BEGIN GPL	
37	SOURCE: s=userSource(id("graphdataset"))	
38	DATA: Time_2=col(source(s), name("Time_2"))	
39	DATA: VO2=col(source(s), name("VO2"))	
40	GUIDE: axis(dim(1), label("Time_2"))	
41	GUIDE: axis(dim(2), label("VO2"))	
42	ELEMENT: line(position(Time_2*VO2), missing.wings())	
43	END GPL.	
44	* Chart Builder.	
45	GGRAPH	
46	/GRAPHDATASET NAME="graphdataset" VARIABLES=Time_2 RQ MISSING=LISTWISE REPORTMISSING=NO	
47	/GRAPHSPEC SOURCE=INLINE.	

Continued on the next page...

	Command	Explanation
48	BEGIN GPL	
49	SOURCE: s=userSource(id("graphdataset"))	
50	DATA: Time_2=col(source(s), name("Time_2"))	
51	DATA: RQ=col(source(s), name("RQ"))	
52	GUIDE: axis(dim(1), label("Time_2"))	
53	GUIDE: axis(dim(2), label("RQ"))	
54	ELEMENT: line(position(Time_2*RQ), missing.wings())	
55	END GPL.	
56	DATASET ACTIVATE $DataSet.	
57	* Chart Builder.	
58	GGRAPH	
59	/GRAPHDATASET NAME="graphdataset" VARIABLES=Time_2 VEBTPS MISSING=LISTWISE REPORTMISSING=NO	
60	/GRAPHSPEC SOURCE=INLINE.	
61	BEGIN GPL	
62	SOURCE: s=userSource(id("graphdataset"))	
63	DATA: Time_2=col(source(s), name("Time_2"))	
64	DATA: VEBTPS=col(source(s), name("VEBTPS"))	
65	GUIDE: axis(dim(1), label("Time_2"))	
66	GUIDE: axis(dim(2), label("VE BTPS"))	
67	ELEMENT: line(position(Time_2*VEBTPS), missing.wings())	
68	END GPL.	
69	FILTER OFF.	Data filtered using the upper and lower limits for VT, VE, VO2, RQ and F_IO_2.
70	EXECUTE.	Filtered values labelled as missing values
71	COMPUTE VO2A=VO2.	
72	EXECUTE.	

Continued on the next page...

	Command	Explanation
73	IF (VtBTPS<270 OR VTBTPS>750 OR VO2<250 OR VO2>710 OR RQ<0.8 OR RQ >1.25 OR VEBTPS>22.5 OR VEBTPS<10)VO2A=-99.	
74	EXECUTE.	
75	Missing Values VO2A(-99).	Formatting of filtered variables defined.
76	RMV /VO2A_1=MEAN(VO2A 10).	Missing value replaced with the mean of the 10 surrounding values.
77		
78	CREATE	Data averaged using a rolling median of 10 values.
79	/VO2A_SM=RMED(VO2A_1 10).	
80	COMPUTE VO2ml.kg.min=VO2A_SM /56.	VO2 ml/min converted to VO2 ml/Kg/min
81	EXECUTE.	
82	GGRAPH	Graph of VO2ml/Kg/min created.
83	/GRAPHDATASET NAME="graphdataset" VARIABLES=Time_2 VO2ml.kg.min[name="VO2ml_kg_min"]	
84	MISSING=LISTWISE REPORTMISSING=NO	
85	/GRAPHSPEC SOURCE=INLINE.	
86	BEGIN GPL	
87	SOURCE: s=userSource(id("graphdataset"))	
88	DATA: Time_2=col(source(s), name("Time_2"))	
89	DATA: VO2ml_kg_min=col(source(s), name("VO2ml_kg_min"))	
90	GUIDE: axis(dim(1), label("Time"))	
91	GUIDE: axis(dim(2), label("VO2ml/kg/min"))	

Continued on the next page...

	Command	Explanation
92	ELEMENT: line(position(Time_2*VO2ml_kg_min), missing.wings())	
93	END GPL.	

B.8.2 Example of PASW filtering and averaging

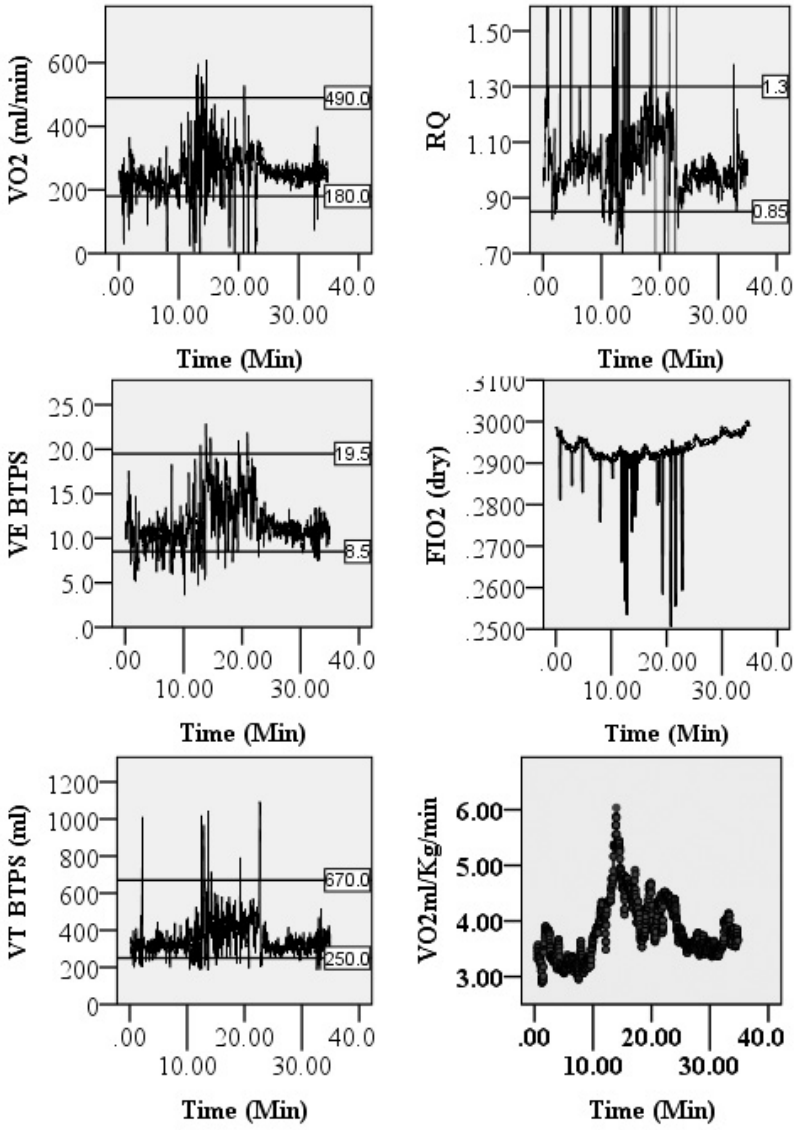


Figure B.1: Medgraphics *Breeze Suite* filtering and averaging graphs.

Appendix C

Publications, abstracts and awards

C.1 Publications

1. Black, C, J., Grocott, M, P., and Singer, M. (2014). Metabolic monitoring in the intensive care unit: a comparison of the Medgraphics Ultima, Deltatrac II, and Douglas bag collection methods. Br J Anaesth, 114(2):616-20.

C.2 Abstracts

1. Black C, J., Grocott M, P., Singer.M. (2011). A Prospective Clinical Comparison of the Medical Graphics Ultima with the Deltatrac II and Douglas Bag Collections. Crit. Care Med., 39(12):90.

2. Black, C, J., Grocott, M, P., and Singer, M. (2012). The feasibility of measuring oxygen consumption during rehabilitation of mechanically ventilated patients. Intensive Care Med, 38(S91).

3. Black, C, J., Grocott, M, P., and Singer, M. (2014) The Oxygen cost of rehabiliation in ICU. Intensive Care Med, 40 (S139).

C.3 Awards

European society of Intensive Care Medicine. Award for the best Nursing/Allied Health Professional abstract at the 2014 Congress.

BJA Advance Access published October 29, 2014

British Journal of Anaesthesia Page 1 of 8
doi:10.1093/bja/aeu365

BJA

Metabolic monitoring in the intensive care unit: a comparison of the Medgraphics Ultima, Deltatrac II, and Douglas bag collection methods

C. Black[1,2]*, M. P. W. Grocott[3,4] and M. Singer[1]

[1] Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, Cruciform Building, Gower Street, London WC1E 6BT, UK
[2] Therapies and Rehabilitation, University College Hospital, London, UK
[3] Integrative Physiology and Critical Illness Group, Faculty of Medicine, University of Southampton, Southampton, UK
[4] Anaesthesia and Critical Care Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

* Corresponding author. E-mail: claire.black.09@ucl.ac.uk

Editor's key points

- Energy requirements are difficult to measure precisely in critically ill intensive care unit patients and are not monitored routinely.
- This small study compared two commercially available metabolic monitors (Medgraphics Ultima and Deltatrac II) with a Douglas bag technique.
- There was poor agreement between readings from the three devices.
- More accurate devices are needed to monitor gas exchange in mechanically ventilated patients.

Background. The accuracy of oxygen consumption measurement by indirect calorimeters is poorly validated in mechanically ventilated intensive care patients where multiple confounders exist. This study sought to compare the Medgraphics Ultima (MGU) and Deltatrac II (DTII) devices, and the Douglas bag (DB) technique in mechanically ventilated patients at rest.

Methods. Prospective comparison of oxygen consumption measurement using three indirect calorimetry techniques in stable, resting mechanically ventilated patients at rest. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), resting energy expenditure (REE), and respiratory quotient (RQ) were recorded breath-by-breath by the MGU over a 30–75 min period. During this time, simultaneous measurements were taken using the DTII, the DB, or both.

Results. While there was no systematic error (bias) between measurements made by the three techniques (VO_2: MGU *vs* DTII 3.6%, MGU *vs* DB 3.3%), the limits of agreement were wide (VO_2: MGU *vs* DTII 33%, MGU *vs* DB 54%).

Conclusions. Resting oxygen consumption values in stable mechanically ventilated patients measured by the three techniques showed acceptable bias but poor precision. There is an important clinical and research need to develop new indirect calorimeters specifically tailored to measure oxygen consumption during mechanical ventilation.

Keywords: indirect calorimetry; mechanical; oxygen consumption; validation studies; ventilators

Accepted for publication: 1 August 2014

Metabolic monitoring is not routinely performed in the intensive care unit (ICU) setting. However, recent studies and reviews have highlighted the likely importance of adequate assessment of energy requirements in mechanically ventilated patients.[1–4] Hypocaloric feeding will potentially exacerbate poor functional outcomes through significant long-term calorie deficits, while overfeeding is associated with higher mortality rates[5] and an increased length of ICU stay.[6 7] Furthermore, a more precise estimation of metabolic activity to prevent over- or underfeeding may improve patient outcomes.[8–10]

An important challenge arises from the difficulty in achieving reliable measurements. Predictive equations used to calculate energy requirements in mechanically ventilated ICU patients show poor agreement against values measured by indirect calorimetry.[11 12] Whole-body oxygen consumption can be measured directly with the pulmonary artery catheter. However, the use of this invasive device has dwindled markedly over the last few years[13] and has inherent errors, including lung oxygen consumption and mathematical coupling.[14] Even if used, the catheter is unlikely to remain *in situ* long after the resolution of shock or during the recovery phase of critical illness to avoid infectious and other complications. Thus, the non-invasive technique of indirect calorimetry, using data obtained from inspired and expired gas analysis, is the most readily available means of measuring oxygen consumption and carbon dioxide production.

The Deltatrac II (DTII, Datex Ohmeda, Finland) has been the most widely used and validated device in the ICU,[15 16] but is no longer manufactured nor supported. Newer devices are currently targeted towards exercise testing in spontaneously

breathing patients and little validation data are available in mechanically ventilated patients. While *in vitro* validation of such devices using lung simulator models is straightforward,[17] *in vivo* validation techniques are far more challenging as mechanical ventilation introduces significant inconsistencies in temperature, humidity, peak airway pressure, expiratory flow rates, and bias flow. We thus decided to compare readings obtained from a currently available device, the Ultima (MGU) manufactured by Medgraphics (St Paul, Minneapolis, MN, USA), with traditional 'reference standards' the DTII, and the Douglas bag (DB) technique, in mechanically ventilated patients at rest.

Methods

Ethical approval was granted for the study (REC reference number: 09/H1307/107) and informed consent or surrogate approval obtained from all patients or their next-of-kin.

Patients undergoing mechanical lung ventilation with stable settings were recruited from the ICU at University College Hospital, London, UK. Patients were excluded if they had burns, endotracheal or tracheal leaks >10%, open chest drainage, an inspired oxygen ($F_{I_{O_2}}$) ≥0.6, were pregnant, <18 yr of age, or had cardiorespiratory instability requiring frequent changes in ventilator settings, $F_{I_{O_2}}$, inotropic, or sedative drug dosages. The measurements were taken simultaneously; therefore, factors such as room temperature and nutritional status were not controlled. The mechanical ventilator used in all studies was the Servo-i (Maquet, Solna, Sweden). Before each test, the DTII and MGU machines were warmed up for 30 min and calibrated in line with the manufacturers' instructions. Patients were clinically stable for 30 min preceding measurement (<20% variation in heart rate, arterial pressure, or oxygen saturation). Mechanical ventilation settings were kept stable over the hour preceding and during the test period.

Oxygen consumption (VO_2), carbon dioxide production (VCO_2), resting energy expenditure (REE), and respiratory quotient (RQ) were recorded breath-by-breath by the MGU over a 30–75 min period. During this time, simultaneous measurements were taken using the DTII, the DB, or both. The tests were repeated, where possible, at different time points over the subsequent month to collect up to three paired measurements per patient using both MGU and DTII, and MGU and DB collection techniques (Fig. 1A and B).

DB collection

This method, first described in 1911 by the Oxford physiologist, Gordon Douglas,[18] has latterly been used to validate measurements made by various metabolic monitors.[19–22] For the current study, gas was collected over three 5 min periods from the expiratory exhaust of the ventilator, into separate pre-labelled 100 litre PVC gas collection bags (Harvard Apparatus Ltd, Edenbridge, UK). Pre-labelled 50 ml syringes and three-way taps were purged with 100 ml of expired gas from the respective gas collection bags, before aspiration of 50 ml of gas for analysis from each bag. Twenty millilitres of this gas were then analysed using a blood gas analyser (ABL735 or 825, Radiometer, Brønshøj, Denmark). Two precision gases; 5% CO_2/55% O_2 (General Electric, Amersham, UK) and 1.5% CO_2/21% O_2 balanced with N_2 (BOC, Windlesham, UK) were used to

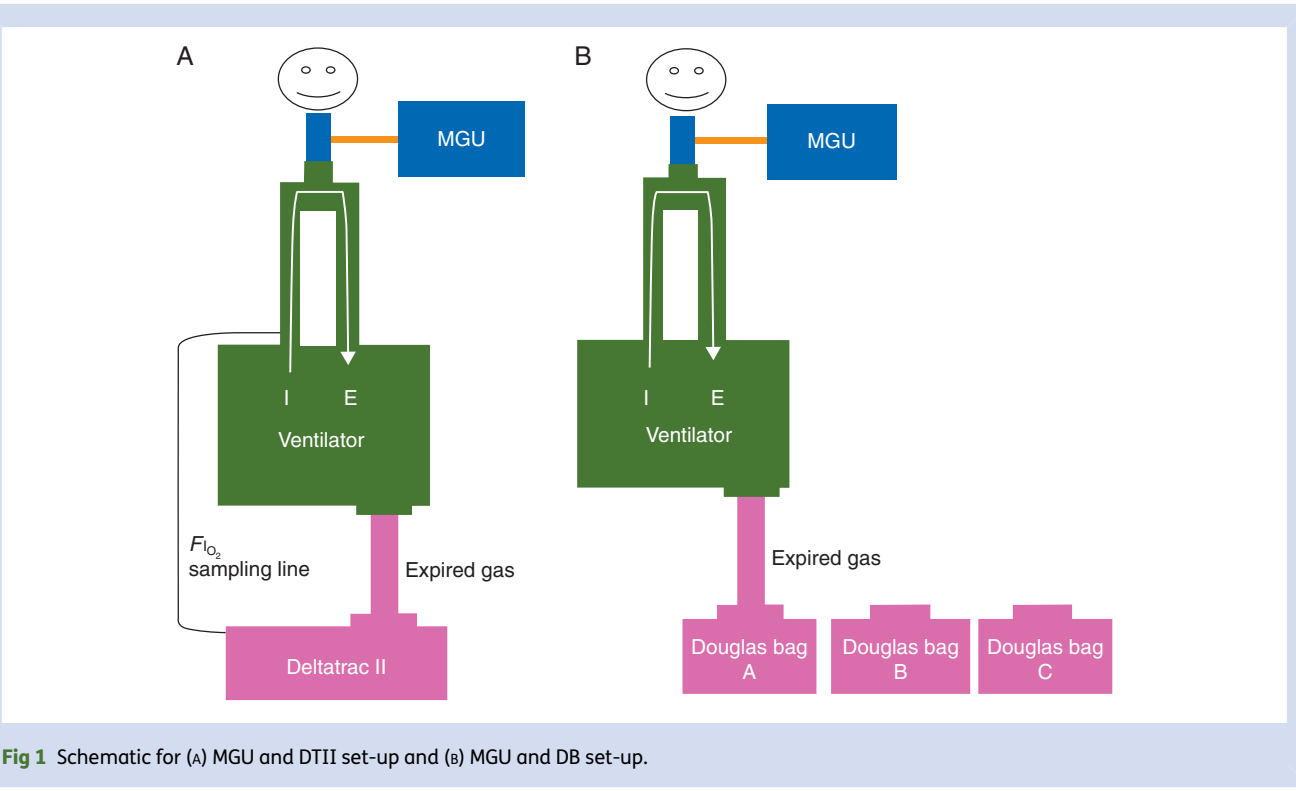


Fig 1 Schematic for (A) MGU and DTII set-up and (B) MGU and DB set-up.

create reference equations for the gas analysers before the study began.

The gas collection bags were emptied using a wall-mounted suction unit set at low flow, through a Harvard dry gas meter (Harvard Apparatus, Holliston, MA, USA) calibrated at the beginning of the study. VO_2, VCO_2, and REE of the DBs were then calculated (Supplementary material SA).

Deltatrac II

First described by Meriläinen,[23] this open-circuit calorimeter has two chambers. The first chamber collects and mixes the gas expired by the patient. Gas is then sampled from this chamber and the fraction of expired O_2 and CO_2 analysed using paramagnetic and infrared analysers, respectively. The expired gas is then drawn through an air dilution chamber at a constant flow rate of ~40 litre min^{-1}. The flow rate and RQ were calibrated using an ethanol burn test before commencement of the study.[24] Gas is sampled from the air dilution chamber and the fraction of CO_2 analysed, allowing calculation of the volume of CO_2 expired by the patient, that is, $VCO_2 = F_{E_{CO_2}} \times 40$ (flow constant). The RQ is derived from a transformation of the Haldane equation with the assumption that nitrogen is neither produced nor retained by the body, and that no gases are present other than O_2, CO_2, and nitrogen. As the DTII measures neither flow nor volume, it is not affected by flow-by.

Data were collected over 1 min intervals. The mean of the values obtained over the first 5 min period where the within-test coefficients of variation of both VCO_2 and VO_2 were $\leq$5% was used in the analysis.[25–27]

Medgraphics Ultima

The MGU measures inspiratory and expiratory flows through a bi-directional flow sensor and therefore does not require the Haldane equation used by most indirect calorimeter devices to calculate inspiratory volumes from expiratory volumes. The oxygen analyser is a fuel cell with a response time <80 ms, while the carbon dioxide analyser is a non-dispersive infrared sensor with a response time <150 ms. The system samples gas continuously and phase aligns O_2 and CO_2 signals with the flow signal to calculate inspired and expired values. *In vitro* validation of the device was carried out jointly by the study group and Medical Graphics UK (Gloucester, Glos, UK) using a lung simulator.[17] The flow sensor was calibrated using a 3 litre syringe and the gas analysers were calibrated with precision gas before each individual test.

Data points within the MGU tests were excluded if the RQ was <0.6 or >1.2, the V_T was <150 ml, or the VO_2 or VCO_2 were <50 ml min^{-1}. Collected data were then averaged as the middle five of seven breaths.

Analysis

Simultaneous MGU recordings were used for comparison against both DTII and DB measurements. Measurements were discarded if the mean RQ value obtained from either the 5 min DTII or the three DB collections were <0.6 or >1.2. Data were to be excluded if the coefficient of variation (COV) was >10% for individual DB collections, in the event, none needed to be excluded or >5% for the DTII tests. All coefficients of variation for the MGU tests were <14%. The Bland–Altman plots (mean measurements made by the two devices *vs* the difference in measurements between the devices) were used to calculate precision and bias. We decided *a priori* that a 30% error was acceptable, as recommended by Critchley and Critchley.[28] This would give $\pm$600 kcal day^{-1} error for a patient consuming 2000 kcal day^{-1}.

Results

Sixteen patients were recruited and tested on 39 occasions. Patient characteristics and ventilator settings for each test are given in Table 1. Comparisons between techniques, number of tests performed, and proportion of excluded tests are shown in Table 2, while the reliability of the individual techniques is shown in Table 3.

The Bland–Altman plots of VO_2, VCO_2, REE, and scatter plots for RQ are presented in Figure 2, with bias and precision (95% limits of agreement) shown in Table 4.

Medgraphics Ultima *vs* Douglas bag

Nineteen valid tests were carried out in nine patients. Although bias was good for VO_2, VCO_2, and REE, precision was weak with wide levels of agreement and a maximum random error of 54% for VO_2, 51% for VCO_2, and 43% for REE. If proportionality of the measurements is taken into account and the percentage error for each individual data set calculated, then the random error is 42% (−27% to 15%) for VO_2, 57% (−17% to 40%) for VCO_2, and 32% (−9% to 23%) for REE (Supplementary material SB).

Medgraphics Ultima *vs* Deltatrac II

Nineteen valid tests were carried out in 10 patients. Overall bias was good for VO_2, VCO_2, and REE; however, yet again, there were wide limits of agreement for all three measures. It was superior to the comparison between MGU and the DB techniques with random errors of 33%, 27%, and 31% for VO_2, VCO_2, and REE, respectively. If proportionality of measurements is taken into account, and the percentage error for each data set calculated, then the random error widens to 41% (−13% to 28%) for VO_2, 31% (2% to 29%) for VCO_2, and 37% (−28% to 9%) for REE (Supplementary material SB).

Discussion

This study describes the unique comparison of a currently available device the Ultima (MGU) with traditional reference standards, the DTII and the DB techniques, in mechanically ventilated patients at rest.

While the systematic error (bias) between the MGU measurements of VO_2, VCO_2, and REE, and both those of the DTII and the DB, was acceptable, the limits of agreement were wide. Comparison between the MGU and the DTII was more acceptable but at the margins of acceptability for the measurement of metabolic activity, either for research or clinical

Table 1 Patient characteristics. $F_{I_{O_2}}$, fraction of inspired oxygen

Patient	Test	Reason for admission	Age	BMI	Gender	Pressure support	PEEP	$F_{I_{O_2}}$
1	1	AAA repair	82	29	M	12	5	0.35
	2					12	5	0.40
2	1	Pneumonia	45	14	F	9	2	0.35
3	1	Gastric resection	79	25.7	F	5	5	0.40
	2					12	5	0.45
	3					12	5	0.45
4	1	Pneumonia	70	30	M	NAVA	5	0.30
	2					NAVA	5	0.30
	3					NAVA	5	0.30
5	1	Pneumonia	71	20	M	13	5	0.25
	2					13	5	0.25
6	1	Coronary artery bypass graft	78	—	M	12	10	0.50
	2					12	10	0.55
	3					6	10	0.45
7	1	Whipple's procedure	66	—	M	10	5	0.30
8	1	Hemi-colectomy	75	21.7	F	13	5	0.35
	2					12	5	0.25
	3					10	5	0.30
9	1	Pancreatitis	79	27.7	M	10	5	0.25
	2					15	5	0.25
	3					0	0	0.28
10	1	Small bowel resection	79	19.7	F	5	5	0.28
	2					5	5	0.28
	3					5	5	0.30
11	1	Thrombotic thrombocyto-penic purpura	58	35	F	10	5	0.30
	2					10	5	0.35
	3					0	5	0.35
12	1	Pleurodesis	76	34	M	8	5	0.30
13	1	Small bowel ischaemia	69	—	F	14	5	0.35
	2					5	5	0.30
	3					0	5	0.30
14	1	Urosepsis and heart failure	74	—	F	20	5	0.40
	2					20	8	0.30
	3					15	5	0.30
15	1	Femoral artery aneurysm	69	—	M	0	5	0.25
	2					0	5	0.30
16	1	Pneumonia and heart failure	61	47.3	M	0	5	0.30
	2					0	5	0.30
	3					5	5	0.30

purposes, albeit assuming the DTII represents an accurate reference standard. There is a remarkable lack of consistency in the criteria deciding comparability between a reference technique and new devices. Using cardiac output measurement techniques as an example, Critchley and Critchley[28] proposed that the accuracy of both devices should be taken into account. Thus, if the reference device, in this case, the DTII, was considered to have an accuracy of $\pm$20% and the test method, in this case, the MGU, a similar accuracy, then the shared limits of agreement would be $\pm$28%.

The MGU is predominantly used in exercise testing in spontaneously breathing patients.[29] Validation for this device is relatively scanty, even in spontaneously breathing subjects. Cooper and colleagues[30] compared the MGU and four other devices against the DTII in resting subjects and found all were inferior in terms of within-patient COV for resting metabolic rate, ranging from 4.8% to 10.9% compared with 3% for the DTII. Other studies in healthy self-ventilating individuals using the Medgraphics CCM Express, a device similar to the MGU, have shown acceptable agreement, although lower absolute values compared with the reference technique.[31 32] VO_2 in mechanically ventilated patients at rest is relatively low (~400 ml min^{-1}), in comparison with the 2–5 litre min^{-1} values seen at peak exercise in ambulant healthy individuals.[33] Therefore, the signal-to-noise ratio is far greater in resting mechanically ventilated patients than that recommended by the exercise testing literature.[34]

Data directly validating indirect calorimetry devices in mechanically ventilated patients are also scarce, despite their promotion as a tool to titrate nutritional input. A recent study[35] in 24 ICU patients reported the mean REE values as 64% higher for the

Table 2 Distribution of tests across patient samples. MGU, Medgraphics Ultima; DB, Douglas bag; DTII, Deltatrac II; RQ, respiratory quotient; COV, coefficient of variation

Comparison	No. of patients tested	No. of tests	No. of tests used	Reason for not using tests
MGU *vs* DB	9	25	19	(1) MGU COV and RQ DB
MGU *vs* DTII	10	24	19	(2) MGU COV and RQ DB (3) MGU COV and DTII RQ (4) DTII COV and RQ DB
Total	16	39	35	4

Table 3 Reliability of the individual techniques. MGU, Medgraphics Ultima; DB, Douglas bag; DTII, Deltatrac II; RQ, respiratory quotient; COV, coefficient of variation

Technique	Unusable data	Reason why unusable
MGU	3 of 39 (7%)	Unstable VO_2
DB	26 of 75 bags collected (34%)	19 RQ unacceptable Six volume loss from DBs One expiratory gas analysis error
DTII	3 of 24 (12%)	Two RQ unacceptable, 1COV error

CCM Express compared against the Deltratrac. Repeated readings from the same instrument gave a COV of 4.1% and 7.9% for Deltatrac and CCM Express, respectively. In the present study, we did not find a systematic bias, although limits of agreement were wide. The coefficients of variation for VO_2 were $<5\%$ between each minute of the 5 min test for the DTII, $<10\%$ between each bag in a single DB collection test, and $<14\%$ for breath-to-breath measurements with the MGU. However, despite our measurements being taken at rest, the pattern of breathing of most patients was irregular. This may have contributed to the intra-device differences, in particular the MGU that measures breath-by-breath, the DT that measures over 1 min, while the DB measure is averaged over a 5 min collection. This is consistent with the lack of bias but poor precision seen between techniques.

Given the high likelihood of a marked day-to-day variability in VO_2 in ICU patients, we felt that repeatability of tests taken over different days could not be reliably assessed. Our pilot data did however demonstrate that COV between repeated tests taken within the same hour in resting patients was between 1% and 9%.

The accuracy of the reference standard must be taken into account. Tissot and colleagues[22] directly compared the DTII with either DB gas collections or mass spectroscopy in 35 mechanically ventilated patients, and found both excellent bias and precision. On the other hand, Takala and colleagues[16] found VO_2 values obtained from the Deltatrac were consistently higher than pulmonary artery catheter-obtained indirect Fick measurements in ICU patients after cardiac surgery. These ranged from 16 (9)% during controlled ventilation, 21 (8)% during synchronized intermittent mandatory ventilation, to 25 (8)% during spontaneous breathing. Levinson and colleagues[36] also found that VO_2 measured by indirect calorimetry (using a DB and mass spectrometry) was 15% higher than that measured by thermodilution in 29 mechanically ventilated patients. In part, this discrepancy may be related to lung oxygen consumption which is not measured by thermodilution and estimated to be 14 (3)% of whole body VO_2.[37] Other studies also report inconsistent findings regarding the accuracy of newer devices compared against the DTII, for example, the M-COVX device.[38–40]

Many of these studies were performed using mechanical ventilators that did not use bias flow (flow-by). This is a continuous flow of gas, usually in the order of 2 litre min^{-1} of the pre-set level of inspired O_2 that is incorporated into most, if not all, modern ventilators. It is delivered through the ventilation circuit and reduces the work of breathing and the sensation of air hunger experienced by the patient during the breath trigger phase of the breathing cycle. Depending on the device being utilized for oxygen consumption, mishandling of this extra volume of oxygen added to the expired volume can significantly impact on the values obtained. Both the MGU and DTII are unaffected by bias flow; the MGU utilizes a flowmeter sited at the tracheal tube within the ventilator circuit, while the DTII measures neither flow nor volume as part of its calculation technique. However, this is a potential source of error for the DB collection or any other device that relies on expiratory volumes. On the other hand, the dead space created by ventilator tubing and heat–moisture exchange systems must be adequately accounted for, so that the MGU correctly phase aligns the flow, oxygen, and carbon dioxide signals.

For reliable measurements, scrupulous attention needs to be paid to the performance of the different techniques, and awareness of the many potential pitfalls. For example, both the DB technique and the indirect calorimetry have multiple potential sources of error (Tables 5 and 6). While every attempt was made to control these errors during this study, the Bland–Altman plots illustrate considerable random rather than systematic error. A 16% measurement error for VO_2 is recognized for the DB technique.[36]

We reduced the potential physiological variability of the tests by performing measurements simultaneously. The possibility that the sampling techniques bias each other was small. The DTII samples inspiratory gas continuously at 150 ml min^{-1} against a mean minute ventilation (MV) of 12 litre min^{-1} giving, at worst, a reduction of 1.25% of minute volume. The MGU samples gas continuously, both during inspiration and expiration, at a maximum of 130 ml min^{-1}, potentially creating a 0.36% inspiratory volume error and a 0.72% expiratory volume error.

The MGU consistently reported greater MV than the Servo-i ventilator. This error can be accounted for in the different ways the gases are described by the respective device; MGU as body temperature and pressure-saturated and Servo-i as

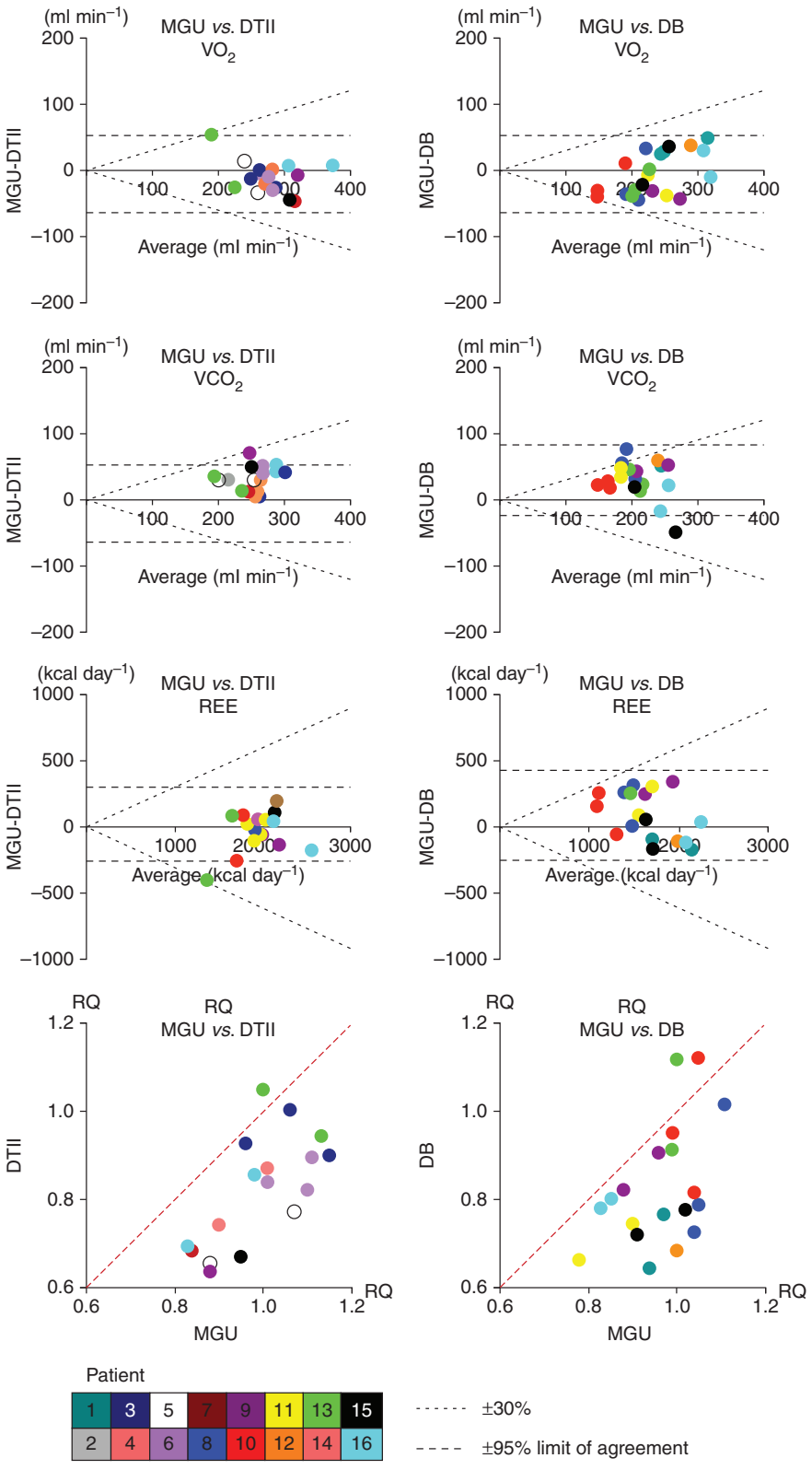


Fig 2 Bland–Altman plots for VO_2 and VCO_2, and scatter plots for RQ for comparisons between the MGU, DTII, and DB techniques. Each colour represents an individual patient. All plots are MGU-the reference device.

Table 4 Precision and bias for VO_2, VCO_2, and REE measurements made between the MGU, DTII, and DB techniques. MGU, Medgraphics Ultima; DB, Douglas bag; DTII, Deltatrac II

Comparison	Parameter	Mean	Bias	Precision	Maximum % error (2 SD μ^{-1})
MGU *vs* DB	VO_2 (ml min^{-1})	231	+7.0	−56 to +70	54
MGU *vs* DTII		272	−10.3	−56 to +35	33
MGU *vs* DB	VCO_2 (ml min^{-1})	208	+31	−22 to 85	51
MGU *vs* DTII		249	+34	−0.6 to 68	27
MGU *vs* DB	REE (kcal day^{-1})	1655	+93	−263 to 449	43
MGU *vs* DTII		1812	+28	−249 to 305	31

Table 5 DB sources of error. VO_2, oxygen consumption; VCO_2, carbon dioxide production; RQ, respiratory quotient; $F_{E_{O_2}}$, fraction of expired oxygen; $F_{E_{CO_2}}$, fraction of expired carbon dioxide

Source of error	VO_2	VCO_2	RQ
For each 0.1 kPa increase in $F_{E_{O_2}}$	−16.42	0	−0.05
%	−6.66	0	—
For each 0.1 kPa increase in $F_{E_{CO_2}}$	−5.34	12.45	0.07
%	−2.17	7.11	—
For each litre increase in volume	4.09	2.91	—
%	1.66	1.66	0
For each 5% increase in humidity	−0.62	−0.44	—
%	−0.25	−0.25	—
For each 0.1% increase in $F_{I_{O_2}}$	15.79	0	−0.08
%	6.41	0	—
For each 0.5°C increase in temperature	−1.43	−0.29	0
%	−0.58	−0.16	—

Table 6 Challenges associated with indirect calorimetry monitoring

Precision and response time of the gas analysers
High pressures within the inspiratory limb of the ventilator circuit
Leaks from the ventilator circuit
High inspired oxygen concentrations
Need for meticulous calibration and for correct ambient conditions entered into the analysis software
Handling of bias flow (flow-by) from the ventilator
Instability of the fraction of inspired oxygen ($F_{I_{O_2}}$) during inspiration
Dead space created by the ventilator tubing and heat–moisture exchange systems

atmospheric temperature and pressure-saturated at 21°C. Of interest, the Servo-i delivers a 10–20% larger breath than most clinicians would expect (Supplementary material SC).

As a clinical tool, changes in VO_2 may be more relevant and reliable than absolute values, for example, in response to a physiological challenge (e.g. sitting on the edge of bed, change of ventilator settings).

Our study enrolled relatively low numbers of patients with a limited range of VO_2, but it serves to highlight some of the issues and pitfalls that must be addressed to develop a metabolic monitoring device that is fit for purpose. Such a device needs to be integrated into a mechanical ventilator, accommodate the challenges of temperature, humidity, dead space, and tidal volume entropy and specifically have precision at low levels of VO_2.

Conclusion

Although showing low bias when compared with the reference methods of the DB technique and the DTII indirect calorimeter, the MGU lacks precision. This may be due in part to limitations of the reference methods. For this field to move forwards, industry must collaborate with clinicians and researchers to improve the accuracy of devices that monitor gas exchange in mechanically ventilated patients.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

C.B.: study design, patient recruitment, data collection, data analysis, and manuscript preparation. M.S.: study supervision and critical review of the manuscript. M.G.: critical review of the manuscript.

Declaration of interest

None declared.

Funding

C.B. is funded by a National Institute for Health Research, Clinical Academic Training Fellowship. This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

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Handling editor: J. P. Thompson